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HIGH LONG-TERM DRUG-FREE REMISSION RATE FOR ACUTE VOGT–KOYANAGI–HARADA DISEASE WITH AN APPROPRIATE IMMUNOSUPPRESSIVE REGIMEN

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Purpose: To report the clinical profile and outcomes of acute Vogt–Koyanagi–Harada disease with a strict immunosuppression regimen and investigate the risk factors for a prolonged disease course.

Methods: A total of 101 patients with acute Vogt–Koyanagi–Harada (202 eyes) with more than 24 months of follow-up were recruited from January 2011 to June 2020. They were divided into two groups according to the interval between the onset of Vogt–Koyanagi–Harada and treatment. Oral prednisone was gradually tapered off by a diminished dose according to a relatively strict protocol. Patient responses to the treatment regimen were classified as long-term drug-free remission or chronic recurrent.

Results: Ninety-six patients (95.0%) achieved long-term drug-free remission without recurrence, while 5 (5.0%) had chronic recurrence. Most patients achieved good best-corrected visual acuity (90.6% ≧20/25). A generalized estimation equation model demonstrated that time of visit, ocular complications, and cigarette smoking were independent risk factors for a longer disease course, and smokers required a higher drug dose and longer treatment course than nonsmokers.

Conclusion: An immunosuppressive regimen with an appropriate tapering speed can lead to long-term drug-free remission in patients with acute Vogt–Koyanagi–Harada. Cigarette smoking significantly affects ocular inflammation.

RETINA 43:1496–1505, 2023

Vogt–Koyanagi–Harada (VKH) disease is a multisystem disorder characterized by ocular inflammation and neurologic, audiovestibular, and dermatological symptoms.[1] It mainly affects non-White; in China, it accounts for 15.9% of uveitis cases.[2] Vogt–Koyanagi–Harada disease typically begins with choroiditis or chorioretinitis, characterized by exudative retinal detachment (ERD) and disk edema. It progresses to anterior uveitis if no appropriate treatment is provided and eventually develops into recurrent generalized granulomatous uveitis, which is refractory to therapy and may result in complications and significantly decreased vision.[3,4] Early and aggressive treatment with systemic high-dose corticosteroids followed by gradual tapering remains the mainstay therapy.[5]

Systemic high-dose corticosteroids can be administered either orally or intravenously, followed by an oral taper.[6,7] Typical oral prednisone regimens range from 1 to 1.2 mg/kg per day, and tapering for approximately 6 months has been recommended for patients with acute VKH disease.[2,5] Patients receiving systemic corticosteroid treatment for <6 months were more likely to have a recurrence and severe vision loss than those treated for >6 months (58.8% vs. 11.1%).[8] A retrospective VKH study reported that 58.6% of acute VKH cases became chronic or chronic recurrent under treatment with intravenous pulse methylprednisolone (1 g daily for 3 days, followed by oral prednisone [≥1 mg/kg] administered daily and tapered ≥6 months).[9] In Brazilian patients, VKH disease became chronic

recurrent in 79% of cases.[10] Thus, an ideal treatment plan is still lacking because a significant proportion of patients cannot achieve a full recovery and experience chronic recurrence. Long-term administration of oral corticosteroids and immunosuppressants to control recurrent inflammation can have a high economic and psychological burden and severe systemic side effects.

Despite the consensus that oral corticosteroid therapy should be prolonged, the corticosteroid tapering protocol remains controversial. In this article, we report a high long-term drug-free remission rate (95%) among 101 patients with new-onset VKH disease treated with corticosteroids with or without immunosuppressants and with a strict diminishing tapering regimen. We also investigated the independent risk factors for prolonged disease course and the relationship between inflammation and cigarette smoking.

Patients and Methods

This retrospective study was based on data of patients with acute VKH disease (time between disease onset and treatment administration ≤2 months) referred to the Tianjin Medical University Eye Hospital with ≥24 months of follow-up from January 2011 to June 2020. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Tianjin Medical University Eye Hospital (2021KY(L)-13). Vogt–Koyanagi–Harada was diagnosed using the revised diagnostic criteria.[11] Ocular inflammation was graded using the Standardization Uveitis Nomenclature guidelines.[12] The following data were entered into a database for statistical analysis: demographic characteristics, detailed history, ophthalmologic examinations, laboratory examination findings, therapeutic regimen, treatment response, complications, and long-term clinical outcomes. The ophthalmologic evaluation included Snellen best-corrected visual acuity (BCVA) and intraocular pressure (IOP) measurement; slit-lamp examination and fundoscopy; and auxiliary examinations including fundus photography, optical coherence tomography (OCT), fundus fluorescence angiography, and indocyanine green angiography.

Visual acuity cutoffs of 20/50 or worse and 20/200 or worse were used according to the Standardization Uveitis Nomenclature Working Group recommendations.[12] Patients with VKH disease were classified into two groups according to the time between uveitis attack and initial evaluation. Group 1 included patients who consulted us within 2 weeks after the uveitis attack, whereas Group 2 included those who started therapy between 2 weeks and 2 months after the attack. The VKH treatment protocol began with oral prednisone 1 to 1.2 mg/kg/day (maximum dosage ≤80 mg/day) administered for 1 week, followed by a gradual reduction of 10 mg per week until a daily dose of 60 mg was reached, and then tapering by 5 mg per week until a daily dose of 40 mg was reached. Thereafter, the tapering interval was extended, and prednisone was decreased by 5 mg every 10 to 14 days to 20 mg/day. Finally, the dose was tapered off by a diminished dose (1.25 mg per 10–14 days) until discontinuation. The dose and interval of corticosteroid tapering were adjusted slightly according to the patients' weight and treatment response. In cases that could be controlled with corticosteroids alone, no additional immunosuppressants were added to prevent further relapse. If patients were intolerant or did not respond well to corticosteroid treatment (no amelioration or worsening of anterior chamber (AC) cells, vitreous haze, and ERD after an initial high dose of corticosteroid) or ocular inflammation was severe (AC cells or vitreous haze ≥grade 3), other immunosuppressants were added (including azathioprine, cyclosporin A [CsA], mycophenolate mofetil [MMF], and methotrexate). Topical corticosteroid eye drops were applied when inflammatory cells were observed in the AC.

Two outcomes were proposed: long-term drug-free remission and chronic recurrence. Long-term drug-free remission was defined as null cells in both the anterior and posterior segments and no recurrence of signs of intraocular inflammation after therapy discontinuation for ≥1 year. Chronic recurrence was defined as the development of recurrent granulomatous inflammation during therapy and therapy could not be stopped completely or ocular inflammation relapse after the termination of all treatments for ≥ 3 months.

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This work was funded by Tianjin Key Medical Discipline (Specialty) Construction Project, Tianjin Science and Technology Support Plan (20YFZCSY00990), Natural Science Foundation of Tianjin (20JCZDJC00100), and Hebei Provincial Administration of Traditional Chinese Medicine Research Project (2022564).

None of the authors has any financial/conflicting interests to disclose.

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Inflammation relapse during therapy was graded as obvious recurrence or slight recurrence. Obvious recurrence was defined as ERD relapse, two-step increase in AC cells, appearance/reappearance of iris nodules or greasy-appearing keratic precipitates, and two-step aggravation of vitreous haze during treatment. Slight recurrence included an increase in AC cells and an increase in the vitreous haze from 0 to 0.5, reappearance of inflammatory cells in the vitreous, or a one-step increase in AC cells and vitreous haze. Medication regimens were adjusted accordingly, including the addition of corticosteroids or immunosuppressants, or slowing down corticosteroid tapering, once any sign of inflammation recurrence emerged.

Patients were followed up 1 week after the therapy started. If the AC cells and ERD improved as expected, the patients were followed up after 1 month of treatment and thereafter once a month until treatment discontinuation. Otherwise, the regimen was adjusted and the patients visited every 2 weeks until satisfactory amelioration of ocular inflammation was achieved.

Twelve months was the cutoff for investigating the factors affecting treatment course length. Clinical factors included age, sex, time of visit, initial extraocular manifestations, initial BCVA, 1-month ERD recovery, ocular complication development (cataract, secondary ocular hypertension [OHT], or choroidal neovascularization), and cigarette smoking. As the association between noninfectious uveitis and cigarette smoking was strong,[13] patients were divided into two subgroups according to cigarette habits to further investigate the prognostic effect of cigarette smoking on patients with VKH disease. Clinical parameters included time of visit, drug withdrawal, treatment course, use of immunosuppressants, immunosuppressant use duration, ERD recovery time, final BCVA, development of sunset glow fundus, and inflammation recurrence.

Statistical analyses were performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY). Snellen BCVA measurements were converted to logarithm of the minimum resolution angle (logMAR) for statistical analysis. A normality test was conducted using the Shapiro–Wilk test. Descriptive statistics included mean and SD for normally distributed continuous variables and median and range for nonnormally distributed variables. Statistical analysis was performed using one-way analysis of variance and Wilcoxon signed-rank tests. Qualitative variables were presented as numbers and percentages and compared using the chi-square test (or Fisher exact test if the chi-square test criteria were not fulfilled). Kaplan–Meier analysis was performed to evaluate the cumulative survival of patients with visual acuity $\geq$20/25 during follow-up. For associated factors of disease duration of more than 12 months, regression analysis was performed using a generalized estimation equation model to adjust for possible intraeye correlation. Univariate generalized estimation equation was performed to identify potential prognostic factors. Multivariate generalized estimation equation model included parameters with P value < 0.10 in univariate regression analysis. Regression coefficients with 95% confidence intervals were presented. Statistical significance was set at $P < 0.05$.

Results

Demographics and Clinical Characteristics

In total, 101 patients (202 eyes) with a median follow-up of 40.0 months (range 24–93 months) were enrolled; 46 (45.5%) were men and 55 (54.5%) were women. The median age at diagnosis was 40.0 years (range 15.0–82.0 years). The main demographic and clinical characteristics are summarized in Table 1.

Treatment Course and Use of Immunosuppressants

Ninety-six patients (95.0%) were tapered off all medications with a median time frame of 11.0 months (range 9.0–41.0 months). Among patients tapered off of all medications, 56 were in Group 1 and 40 were in Group 2; the median time frame was 11.0 months (range 9.0–30.0 months) in group 1 and 12.0 months (range 9.0–41.0 months) in group 2 (P = 0.240).

Eleven patients (18.6%) in Group 1 and 6 patients (14.3%) in Group 2 were administered immunosuppressants to reduce corticosteroids as requested by patients, whereas immunosuppressants were added to 13 patients (22.0%) in Group 1 and 18 patients (42.9%) in Group 2 because of poor response to isolated corticosteroid therapy (P = 0.025). Among the 48 patients (47.5%) on immunosuppressants, one immunosuppressant was used in 39 patients (81.3%) and two immunosuppressants in nine patients (18.8%). Of the patients using one immunosuppressant, the numbers of patients on CsA, azathioprine, methotrexate, and MMF were 23, 2, 6, and 8, respectively. Of the patients requiring two immunosuppressants, all used CsA, two combined with azathioprine, three combined with methotrexate, and four combined with MMF. Immunosuppressant dosages were as follows: CsA 1.5 to 2.5 mg/kg/day, azathioprine 1 to 2 mg/kg/day, methotrexate 10 to 15 mg/week, and MMF 0.75 to 1.0 g daily.

Treatment Response

Ocular inflammation was well controlled in both groups. All patients showed remission of intraocular

Table 1. Main Demographic Characteristics and Clinical Manifestations of Patients With VKH Disease

Characteristics	Total	Group 1	Group 2	*P*
Patients/eyes	101/202	59/118	42/84	—
Age (M-R)	40.0 (15.0–82.0)	40.0 (23.0–82.0)	41.0 (15.0–67.0)	0.909
Male/female	46 (45.5%) /55 (54.5%)	25 (42.4%) /34 (57.6%)	21 (50.0%) /21 (50.0%)	0.448
Time to visit (day) (M-R)	12.0 (1.0–60.0)	7.0 (1.0–14.0)	30.0 (15.0–60.0)	<0.001
IOP at baseline (mmHg) (M-R)	13.8 (7.6–41.0)	14.3 (7.7–41.0)	13.0 (7.6–28.4)	0.149
Extraocular manifestations (cases, %)				
Meningismus	60 (59.4)	40 (67.8)	20 (47.6)	0.042
Audiovestibular symptoms	46 (45.5)	29 (49.2)	17 (40.5)	0.388
Hyperesthesia	36 (35.6)	23 (39.0)	13 (31.0)	0.406
Integumentary findings*	3 (3.0)	1 (1.7)	2 (4.8)	0.469
Anterior segment (eyes, %)				
Aqueous cells	151 (74.8)	75 (63.6)	76 (90.5)	<0.001
Anterior chamber cell grade (M-R)	1.0 (0.0–3.0)	0.5 (0.0–2.0)	1.0 (0.0–3.0)	<0.001
Dust-like KPs	12 (6.0)	6 (5.1)	6 (14.3)	0.758
Mutton-fat KPs	6 (3.0)	2 (1.7)	4 (4.8)	0.236
Iris nodules	10 (5.0)	2 (1.7)	8 (9.5)	0.028
Iris synechiae	4 (2.0)	0	4 (4.8)	0.029
Posterior segment (eyes, %)				
Vitritis	101 (50.0)	41 (34.7)	60 (71.4)	<0.001
Vitreous opacity grade (M-R)	0.5 (0.0–3.0)	0.0 (0.0–2.0)	1.0 (0.0–3.0)	<0.001
Choroiditis	200 (100)	86 (100)	114 (100)	—
Optic disk edema	112 (55.4)	65 (55.1)	47 (56.0)	0.903
Retinal detachment	191 (94.6)	116 (98.3)	75 (89.3)	0.006
OCT characteristic (eyes, %)				
Fluctuation of ILM	84 (41.6)	54 (45.8)	30 (35.7)	0.153
Membrane structure	61 (30.2)	48 (40.7)	13 (15.5)	<0.001
RPE fold	104 (51.5)	64 (54.2)	40 (47.6)	0.354
PED	4 (2.0)	3 (2.5)	1 (1.2)	0.643
VKH diagnosis (cases, %)				
Complete	3 (3.0)	1 (1.7)	2 (4.8)	0.593
Incomplete	62 (61.4)	38 (61.0)	24 (57.1)	
Probable	36 (35.6)	20 (33.9)	16 (38.1)	
Outcomes at study deadline (cases, %)				
Restitution and integrum	96 (95.0)	56 (94.9)	40 (95.2)	1.0
Recurrence	5 (5.0)	3 (5.1)	2 (4.8)	

Group 1: treatment started within 2 weeks after the attack. Group 2: treatment started between 2 weeks and 2 months after the attack.
*Integumentary findings include alopecia, poliosis, and vitiligo.
ILM, internal limiting membrane; M, median; PED, pigment epithelial detachment; R, range; RPE, retinal pigment epithelium.

inflammation. Ninety-six patients (95%, 56 patients in group 1 and 40 patients in group 2) achieved long-term drug-free remission (tapered off all medications without recurrence during ≥1 year of follow-up [median, 26 months; range 12–78 months)], and five patients (5%, three patients in group 1 and 2 patients in group 2) developed chronic recurrence and maintained or reused corticosteroids and immunosuppressants because of persistent or recurrent inflammation. As shown in Figure 1, a patient had no recurrence of inflammation after discontinuation of the drug during a follow-up of 18 months.

During the treatment course, inflammation recurrence was observed in 29 patients (30.2%) with long-term drug-free remission, including 11 patients (19.6%) in group 1 with 23 episodes and 18 patients (45.0%) in group 2 with 37 episodes ($P = 0.008$). Specifically, obvious recurrence was observed in 5 cases (8.5%) in group 1 and 8 cases (19.0%) in group 2. Slight recurrence was found in 9 cases (15.3%) in group 1 and 16 cases (38.1%) in group 2. In cases of obvious recurrence, the median number of recurrences was one episode (range 1–3 episodes) in group 1 and one episode (range 1–4 episodes) in group 2 ($P = 0.943$). Among patients with slight recurrence, the median number of recurrences was one episode (range 1–3 episodes) and one episode (range 1–4 episodes) in groups 1 and 2, respectively ($P = 0.677$).

During treatment with prednisone, hyperglycemia and hypertension occurred in nine (8.9%) and six

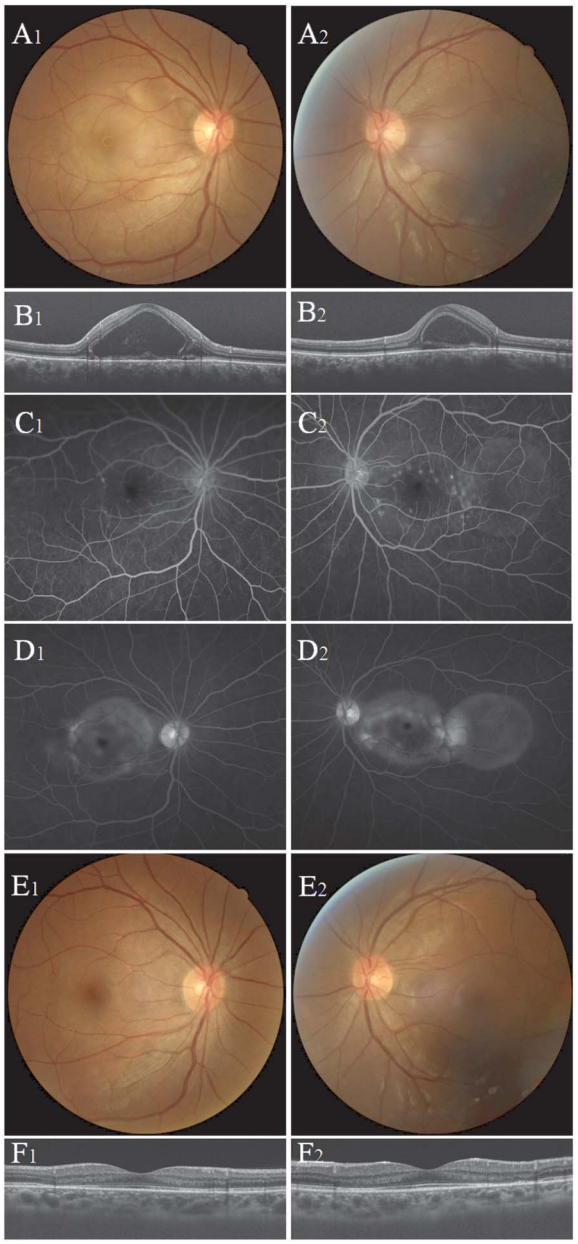

Fig. 1. A 35-year-old male patient complained of acute bilateral decrease in vision for 2 days. BCVA at presentation was 20/40 in the right eye (RE) and 20/50 in the left eye (LE). The bilateral anterior chamber and vitreous body were quiet. Color fundus photographs showed bilateral, bullous retinal detachment (**A_1** & **A_2**). Optical coherence tomography demonstrated large serous neurosensory retinal detachment areas with membranous structures (**B_1** & **B_2**). Fluorescein angiography showed a number of punctate hyperfluorescent dots in the early stage (**C_1–C_2**) and pooling of the dye in areas of an ERD in the late phase (**D_1–D_2**). The patient was treated with oral prednisone (initial dosage at 1 mg/kg/day) for 9 months. On termination of treatment, visual acuity was 20/20 in both eyes without intraocular inflammation. No sunset glow fundus developed (**E_1–E_2**) and OCT demonstrated a normal retinal structure in all layers (**F_1–F_2**). The patient had no recurrence of inflammation after discontinuation of the drug during a follow-up of 18 months and stopped follow-up thereafter.

patients (5.9%), respectively. All side effects gradually subsided with the tapering of prednisone. Five patients (10.4%) using immunosuppressants had mild increases in aminotransferases, which was resolved after the reduction of the immunosuppressant dose.

Visual Outcomes and Ocular Complications

Best-corrected visual acuity values at initial and final visits are summarized in Table 2. Kaplan–Meier survival analysis showed the following proportions of eyes with 20/25 or better at different time intervals after treatment in Groups 1 and 2, respectively: 62.7% and 57.1% after 1 month, 88.1% and 88.1% after 3 months, 91.5% and 88.1% after 6 months, and 96.6% and 90.5% after 1 year (Figure 2).

Sunset glow fundus was observed in 93 eyes (46%, 51 eyes [43.2%] in Group 1 and 42 eyes [50.0%] in Group 2) during the follow-up. The most common complication was cataract, in 26 eyes (12.9%, 8 [6.8%] in Group 1 and 18 [21.4%] in Group 2), 10 of which underwent cataract surgery. Ocular hypertension was observed in 10 eyes (5.0%, 4 [3.4%] in Group 1 and 6 [7.1%] in Group 2) and median IOP was 28.6 mmHg (range 24.4–60.0 mmHg). Steroid-induced open-angle OHT was seen in two eyes and was controlled after the reduction of topical corticosteroid eye drops and the use of IOP-lowering eye drops. Inflammation-induced open-angle OHT occurred in two eyes at the time of significant recurrence, and IOP returned to normal with immunosuppressive drugs and IOP-lowering eye drops. Four eyes exhibited OHT associated with the shallow AC and angle closure at the first visit, which was restored with immunosuppressive therapy. One patient presented to the clinic after 1 week with shallow AC, angle closure, and OHT in both eyes. Intraocular pressure was controlled with systemic and topical IOP-lowering medications and peripheral iridectomy. Choroidal neovascular was found in one eye (0.5%), and no additional therapy was applied because no retinal edema occurred and the choroidal neovascularization was stable over the follow-up.

Changes of Retinal and Choroidal Thicknesses

For 79 patients (78.2%), OCT was performed with the same swept-source optical coherence tomography device (DRI OCT Atlantis, Tokyo, Japan). Retinal and choroidal thicknesses were measured. The mean retinal thickness of macular fovea at the initial visit in groups 1 and 2 was 539.7 and 455.3 μm, with a median of 458.0 μm (range 211.0–1,217.0 μm) and 383.0 μm (range 203.0–1,120.0 μm), respectively ($P = 0.013$). The mean

Table 2. Visual Acuity Distribution in Two Groups

BCVA*	Group 1		Group 2	
	Initial Visit, %	Final Visit, %	Initial Visit, %	Final Visit, %
<20/200	9 (7.6)	0	16 (19.0)	0
20/200–20/40	83 (70.3)	4 (3.4)	39 (46.4)	3 (3.6)
20/40–20/25	18 (15.3)	5 (4.2)	14 (16.7)	7 (8.3)
≥ 20/25	8 (6.8)	109 (92.4)	15 (17.9)	74 (88.1)
Vision (logMAR; M-R)	0.60 (0.00–2.00)	0.00 (0.00–0.60)	0.52 (0.00–2.00)	0.00 (0.00–1.00)
P value†	<0.001		<0.001	

Group 1: treatment started within 2 weeks after the attack. Group 2: treatment started between 2 weeks and 2 months after the attack.
*Best corrected visual acuity in the Snellen chart and logMAR visual acuity chart.
†Statistical differences in BCVA at initial and final visit within each group.
logMAR, logarithm of the minimum resolution angle; M, median; R, range.

retinal thickness of macular fovea at the final visit in groups 1 and 2 was 222.6 ± 23.6 μm (range 174.0–278.0 μm) and 215.3 ± 25.2 μm (range 150.0–275.0 μm), respectively ($P = 0.069$). The mean subfoveal choroidal thickness (SFCT) at the initial visit in groups 1 and 2 was 473.7 and 453.8 μm, with a median of 438.0 μm (range 318.0–905.0 μm) and 406.0 μm (range 295.0–858.0 μm), respectively ($P = 0.033$). The mean SFCT at the final visit in groups 1 and 2 was 252.4 ± 64.1 μm (range 101.0–374.0 μm) and 249.0 ± 48.9 μm (range 135.0–331.0 μm), respectively ($P = 0.578$). Mean retinal thickness of macular fovea and SFCT before and after treatment were significantly different ($P < 0.001$) in both groups (Figure 3).

Prognostic Analysis

The univariate analysis revealed that sex, time of visit, initial BCVA, ocular complications, and cigarette smoking correlated with the treatment course (Table 3), and multivariate analysis confirmed that time of visit ($P = 0.016$), ocular complications ($P = 0.017$), and cigarette smoking ($P = 0.003$) were independent prognostic factors for a longer treatment course (Table 4).

There was no difference in time from VKH onset to the first medical visit depending on smoking (Table 5). Inflammation recurrence was observed more often in smokers than in nonsmokers ($P < 0.001$), and they required significantly more treatment ($P < 0.001$), including the total treatment time and percentage of immunosuppressants added.

Discussion

In this article, we established therapeutic regimens and evaluated long-term outcomes in 101 patients with acute VKH disease. Our results indicate that early identification and appropriate treatment can halt disease progression and lead to a high long-term drug-free remission rate of acute VKH disease.

A high dose of corticosteroids rapidly inhibits intraocular inflammation in patients with acute VKH disease.[6,7,10,14,15] Although there are well-established initial treatment strategies for acute VKH disease, there is a lack of consensus regarding the tapering schedule, which is most directly associated with recurrence rate and visual prognosis.[8,16] The main reason for early discontinuation of treatment was apparent control of active intraocular inflammation; however, some studies showed that the recurrence rate of acute VKH disease was 25% to 75% with a minimum corticosteroid treatment duration of 3 to 6 months.[10,14,17,18] Indocyanine green angiography proved that the recurrent subclinical choroidal inflammation could be detected in many patients at the end of the tapering period even no inflammation could be found on clinical examination.[19,20] Recently, several studies suggested that adding immunosuppressants early is associated with good clinical results in VKH disease[9,21,22,23]; however, a study on acute VKH disease reported that MMF combined with corticosteroids as the first-line therapy could only prevent

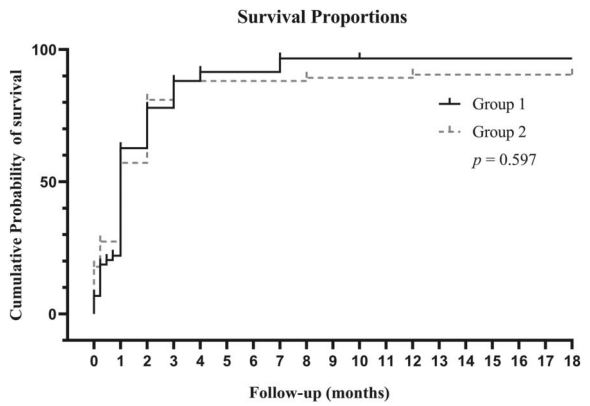

Fig. 2. Kaplan–Meier analysis for patients with BCVA ≥20/25. For patients receiving treatment within 2 weeks of disease onset (Group 1), 96.6% achieved BCVA ≥20/25 at 7 months. For patients receiving treatment between 2 weeks and 2 months of disease onset (Group 2), 90.5% achieved BCVA ≥20/25 at 12 months.

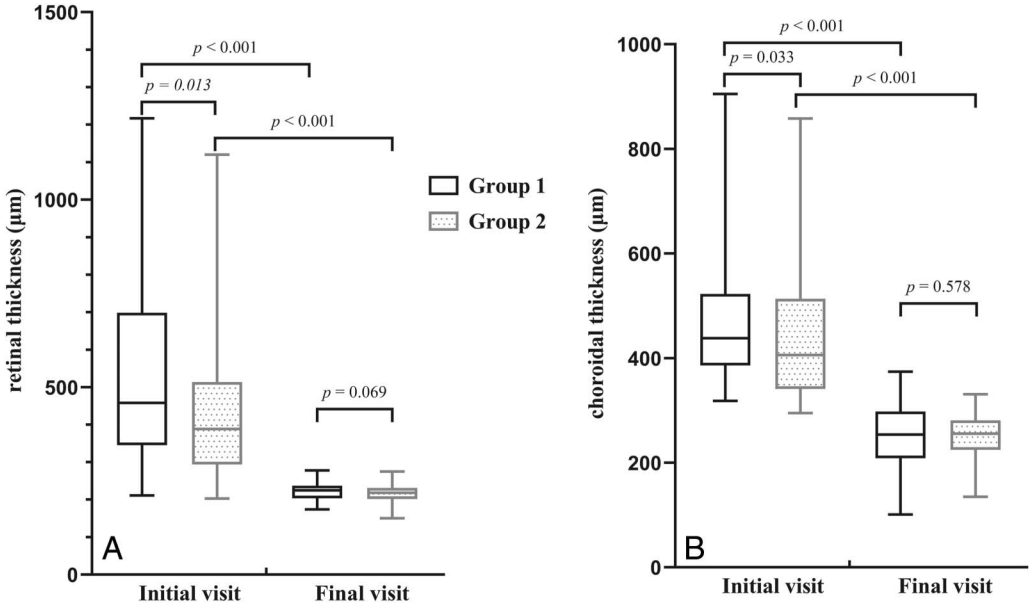

Fig. 3. Changes of retinal and choroidal thicknesses. **A.** Changes of retinal thickness at the macular fovea of two groups at the initial and final visit. The retinal thickness at the macular fovea was statistically different at the initial and final visit in patients from group 1 and group 2 ($P < 0.001$). **B.** Changes of the SFCT of two groups at the initial and final visit. The SFCT was statistically different at the initial and final visit in patients from group 1 and group 2 ($P < 0.001$).

inflammation relapse in 57.9% of patients after the cessation of treatment.[22] Vogt–Koyanagi–Harada disease is significantly associated with longer therapy, more ocular complications, and poorer visual prognosis once it reaches the chronic recurrent stage.[15] Therefore, a reliable medication tapering regimen is necessary to decrease the recurrence rate of VKH.

The therapeutic protocol used in this study aimed to eradicate inflammation and cure VKH disease. Systemic corticosteroids were used as the first-line therapy, and immunomodulatory agents were added only as clinically indicated. The core concept of this regimen includes the following: 1) initiation of a full dose of oral corticosteroids at the onset to completely eliminate intraocular inflammation and restore the normal structure of the retina rapidly; 2) reduction of corticosteroids with diminishing tapering speed to prevent inflammation recurrence; 3) close follow-up to adjust the dosage or tapering speed of oral medicine promptly once any slight signs of inflammation emerge; 4) addition of immunosuppressants if necessary; and 5) maintenance of no signs of ocular inflammation, specifically zero cells in the AC, for ≥3 months before drug withdrawal. In most patients, this schedule maintains zero ocular inflammatory cells until the end of therapy after initial inflammation control. In cases with inflammation recurrence during treatment, timely therapeutic regimen adjustment usually ensures the elimination of the inflammation in most cases. A high long-term drug-free remission rate (95%) in VKH disease was achieved using this regimen, with a median time of 11 months. At a sufficiently long follow-up (≥12 months) after medication cessation, no patients experienced ocular inflammation relapse. Yang et al[21] also reported a low recurrence rate of acute VKH disease using 0.6 to 0.8 mg/kg/day prednisone combined with other immunosuppressive agents, which were slowly tapered off after ≥12 months. This study and the results from the study by Yang suggest that acute VKH disease is curable with an appropriate immunosuppressive regimen. Moreover, the tapering speed after remission of acute inflammation might be essential for the long-term prognosis of initial onset VKH.

Five patients (5.0%) in this cohort developed chronic recurrent disease; all were insensitive to the initial isolated high-dose oral prednisone treatment and were believed to be glucocorticoid-resistant, which might be caused by genetic defects in glucocorticoid receptor isoforms.[24,25] Even with the addition of immunosuppressants, inflammation was not fully controlled. Early initiation of immunomodulatory therapy or the use of biological agents may be useful in such cases.

The window of opportunity for treatment (in which the outcomes can be greatly improved) has been defined as approximately 2 weeks after the onset of initial VKH disease.[17,26,27] We extended this period to 2 months, and most patients (40 cases [95.2%]) who received therapy between 2 weeks and 2 months after

Table 3. Univariate Analysis of 10 Parameters Between Subgroups With Disease Duration More Than and No More Than 12 months

Characteristics	Group with More than 12 months Disease Course (N = 27, Eyes = 54)	Group with No More than 12 months Disease Course (N = 74, Eyes = 148)	*P*
Median age (years)	41.0 (range 15.0–67.0)	40.0 (range 22.0–82.0)	0.912
Sex (male/female)	16/11	30/44	0.098
Time to visit, %			
Within 2 weeks	10 (37.0)	49 (66.2)	0.010
2 weeks–2 months	17 (63.0)	25 (33.8)	
Initial BCVA* (eyes, %)			
<20/200	14 (25.9)	11 (7.4)	
20/200–20/40	30 (55.6)	92 (62.2)	0.068
20/40–20/25	5 (9.3)	27 (18.2)	
≥20/25	5 (9.3)	18 (12.2)	
Recovery of ERD within 1 month (eyes)	42 (77.8)	124 (83.8)	0.483
Ocular complications† (eyes)	24 (44.4)	8 (5.4)	<0.001
Extraocular manifestations			
Meningismus	15 (55.6)	45 (60.8)	0.634
Audiovestibular symptoms	14 (51.9)	32 (43.2)	0.443
Hyperesthesia	12 (44.4)	24 (32.4)	0.267
Cigarette smoking	14 (51.9)	9 (12.2)	<0.001

*Best corrected visual acuity in Snellen chart.
†Complications include cataracts, secondary OHT, and choroidal neovascularization.

onset also achieved long-term drug-free remission and got a satisfying visual prognosis, although they required longer treatment period ($P = 0.240$), had a higher ratio of immunosuppressant usage ($P = 0.025$), and underwent more inflammation recurrence episodes ($P = 0.008$). Previous studies have provided visual acuity indicators in VKH prognosis analysis, including BCVA at the initial visit, ocular complications, and "sunset glow" fundus.[14,21,28] Our ultimate objective was not only to evaluate BCVA improvement but also to taper off all medications without recurrence. Therefore, because most patients without recurrence achieved good BCVA, the risk factors for prolonged treatment course were evaluated using generalized estimation equation. Time of visit ($P = 0.016$), ocular complications ($P = 0.017$), and cigarette smoking ($P = 0.003$) were independent risk factors for a longer treatment course. Cigarette smoking significantly affects ocular inflammation, resulting in increased inflammation recurrence ($P < 0.001$) and drug dosage ($P < 0.001$), and treatment duration ($P < 0.001$). Therefore, early diagnosis, timely and appropriate treatment, and avoidance of cigarette smoking are crucial for shortening the treatment course of acute VKH.

Cigarette smoking has a detrimental influence on human health and is associated with noninfectious uveitis.[13,29,30] Consequently, all patients were divided into smoking and nonsmoking subgroups. The smoking subgroup required a higher drug dosage and longer treatment cycles. Further investigation is needed to clarify the pathologic mechanisms underlying the effects of smoking on uveitis.

Table 4. Multivariate Analysis About the Independent Risk Factors of Disease Course With More Than 12 months

Characteristics	OR	95% CI	*P*
Sex (male/female)	0.987	0.356–2.735	0.980
Time to visit			
<2 weeks	1	—	—
2 weeks–2 months	4.050	1.296–12.651	0.016
Initial BCVA*			
<20/200	1	—	—
20/200–20/40	0.784	0.236–2.601	0.691
20/40–20/25	0.748	0.138–4.064	0.736
≥20/25	0.763	0.113–5.142	0.781
Ocular complications	5.844	1.372–24.897	0.017
Cigarette smoking	6.640	1.938–22.753	0.003

OR, odds ratio; CI, confidence interval.
*Best corrected visual acuity in Snellen chart.

Table 5. Comparison Between the Smoking and Nonsmoking Subgroups

Characteristics	Smoking (N = 23)	Nonsmoking (N = 78)	*P*
Time to visit (days) (M-R)	13.0 (2.0–60.0)	12.0 (1.0–60.0)	0.706
Inflammation recurrence (cases, %)	14 (60.9)	20 (25.6)	<0.001
Treatment time (months) (M-R)	19.0 (9.0–41.0)	11.0 (9.0–30.0)	<0.001
Use of immunosuppressant (cases, %)	18 (78.3)	30 (38.5)	<0.001
Duration of immunosuppressant (months) (M-R)	14.0 (6.0–29.0)	10.0 (4.0–27.0)	0.175
Tapering off all medication (cases, %)	19 (82.6)	77 (98.7)	0.009
Recovery time of ERD (months) (M-R)	1.0 (0.0–2.5)	1.0 (0.0–4.0)	0.074
Sunset glow fundus (cases, %)	14 (60.9)	33 (42.3)	0.117
Final visual (logMAR) (M-R)	0.0 (0.0–0.6)	0.0 (0.0–1.0)	0.052

M, median; R, range.

In conclusion, we established a simple, safe, and effective therapeutic regimen for acute VKH disease, which achieved a high long-term drug-free remission rate. This study had several weaknesses, including that it was a single-center and retrospective study. In addition, no other therapy regimens were tried and compared with that we proposed. However, we believe that different initial therapeutic strategies may all work if the tapering speed is controlled based on close follow-up of inflammatory changes after the remission of acute inflammation. Randomized controlled clinical trials are needed to compare the efficacy and safety of different protocols.

Key words: Vogt–Koyanagi–Harada disease, uveitis, corticosteroid, risk factors, smoking.

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