Original Article

Adalimumab treatment for chronic recurrent Vogt-Koyanagi-Harada disease with sunset glow fundus: A multicenter study

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Abstract:

PURPOSE: We investigated the efficacy and safety of adalimumab (ADA) treatment for chronic recurrent Vogt-Koyanagi-Harada (VKH) patients with sunset glow fundus (SGF).

METHODS: Medical records of 50 chronic recurrent VKH patients with SGF who received ADA treatment for more than 6 months were retrospectively reviewed.

RESULTS: The mean age of chronic recurrent VKH patients with SGF was 55.9 ± 14.4 years, and the male/female ratio was 26/24. Before ADA treatment, the mean daily dose of systemic corticosteroids was 16.5 ± 12.7 mg, and 22 patients (44%) were under immunosuppressors. LogMAR visual acuity (VA), flare counts, subfoveal choroidal thickness (SFCT), indocyanine green angiography scores, and corticosteroid and cyclosporine doses were significantly reduced by ADA treatment at 6 months compared to baseline. Among all parameters, flare count was significantly related to LogMAR VA. LogMAR VA was significantly related to flare counts but not to SFCT nor to ICGA scores. ADA treatment was continued in 94%.

CONCLUSION: ADA was shown to be effective in achieving remission of chronic recurrent VKH disease with SGF refractory to conventional treatments, and was generally well tolerated with few serious adverse events.

Keywords:

Adalimumab, chronic recurrent Vogt-Koyanagi-Harada disease, noninfectious uveitis, sunset glow fundus, TNF inhibitors

Introduction

Vogt-Koyanagi-Harada (VKH) disease occurs secondary to an autoimmune response targeting melanocyte-abundant tissues, such as the eye, inner ear, meninges, skin, and hair.[1] Ocular manifestations are indicated by bilateral granulomatous panuveitis following choroidal stromal inflammation, accompanied by neurological and/or auditory symptoms.[2,3] Ocular features at the initial onset consist of choroiditis with diffuse thickening, spreading to the adjacent structures, and inducing serous retinal detachments and hyperemia of the optic disk.[2] Thereafter, panuveitis with iridocyclitis develops. An autoimmune response against melanin-related proteins in melanocytes in tissues is accounted for the pathogenesis.[4] Human leukocyte antigen (HLA)-DR4/*HLA-DRB1**04 is strongly associated with VKH patients, and genetic factors also influence the development of the disease,[5] but the trigger has remained unclear.

VKH disease is clinically classified into two distinctive stages: initial-onset acute versus chronic recurrent disease.[6] The standard regimen for initial-onset VKH disease is the aggressive use of combined steroidal and nonsteroidal immunosuppression for prolonged periods immediately given at the onset of treatment.[6,7] However, in some proportion of

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VKH patients, even if aggressive immunosuppressive therapy is provided since the beginning, exacerbation occurs during slow tapering of systemic corticosteroids therapy because it was not associated with nonsteroidal immunosuppression. Alternatively, the emergence of side effects of corticosteroids, such as diabetes, osteoporosis, and gastrointestinal ulcers, and, more rarely corticosteroid-induced psychosis, interferes with the continuation of treatment of corticosteroids, and urgent tapering is required. When sufficient control over inflammation and/or clinical quiescence is not achieved,[8-10] the disease progresses to the chronic recurrent stage. The clinical signs, at the ocular level, comprise chronic granulomatous anterior uveitis, sunset glow fundus (SGF) defined as progressive fundus depigmentation, peripheral atrophic foci which represent scars of Dalen-Fuchs nodules, and pigment migration.[11]

Tumor necrosis factor α (TNFα) is a proinflammatory cytokine produced by various cells, including T-cells and macrophages.[12-14] Approximately 20 years ago, TNF inhibitors were gradually used for severe posterior and panuveitis. Adalimumab (ADA; AbbVie, North Chicago, IL, USA) is one of the TNF inhibitors, and the efficacy of ADA treatment for VKH patients resistant to conventional therapy has been demonstrated.[15-26] Recently, we have retrospectively investigated 70 VKH patients who received ADA treatment for more than 6 months in a multicenter study, and found that remission of ocular inflammation in VKH patients resistant for conventional immunosuppressive therapy was effectively achieved and maintained by ADA treatment.[27] In this study, as a subanalysis of the multicenter study, we focused on chronic recurrent VKH patients with SGF and investigated the therapeutic effects of ADA on recurrent uveitis.

Methods

Study design

This is a retrospective, multicenter cohort study evaluating the efficacy and safety of ADA treatment for chronic recurrent VKH patients with SGF. Twelve facilities (National Defense Medical College, Hokkaido University, Tokyo Medical University, Hiroshima University, Kobe University, Saitama Medical Centre of Jichi Medical University, University of Tokyo, Yokohama City University, and Yodogawa Christian Hospital participated in this study. The Centre for Ophthalmic Specialized Care, Lausanne, participated in the design of the study. The medical records of chronic recurrent VKH patients with SGF in the Japanese centers were followed for more than 6 months after the initiation of ADA due to exacerbation and/or relapse of ocular inflammation between April 2016 and March 2020 were retroactively reviewed. The study was conducted according to the tenets of the Declaration of Helsinki and was approved by the institutional review board of each of the ten facilities. The study protocol was described to all human subjects by opt-out method, and written informed consent was waived by the ERB due to the retrospective nature of the study. The criteria and classification of VKH disease by the previous reports[28,29] were used to diagnose VKH patients. Exclusion criteria were the presence of corneal diseases, primary glaucoma, exfoliation syndrome, history of trauma or vitrectomy, history of other uveitis, other systemic inflammatory diseases, or malignancy.

All patients reviewed in this study were Japanese and were diagnosed as chronic recurrent VKH patients with SGF.

Adalimumab treatment

All patients initially received subcutaneous ADA 80 mg, and 40 mg 1 week after the initial administration. Three weeks after the initial administration, 40 mg was subcutaneously injected once every 2 weeks. ADA was administered only for VKH patients, in whom interferon-gamma release assay test and/or tuberculin skin test were negative, following the instructions of the manufacturer.

Outcome measures

Best-corrected visual acuity (BCVA), LogMAR visual acuity (VA) converted from BCVA, flare counts analyzed by laser flare photometry, subfoveal choroidal thickness (SFCT) measured by enhanced depth imaging optical coherence tomography (EDI-OCT) measurements, indocyanine green angiography (ICGA) scores, systemically administrated corticosteroids and immunosuppressors at baseline and 6 months (M) after the initiation of ADA, and side effects of ADA were recorded. VKH disease is a bilateral uveitis, and even if ocular inflammation is clinically observed in only the unilateral eye, binocular abnormalities are usually depicted by ICGA.[30-32] Therefore, the analysis of ocular findings was performed in both eyes.

Aqueous flare counts

Aqueous flare was measured using the Kowa FM 700 LFP (Kowa Company Ltd., Nagoya, Japan).[33] Eight times were taken for each eye and averaged after excluding the minimum and maximum measurements in each series of counts. A single average count for each eye was produced.

Measurement of subfoveal choroidal thickness

The EDI-OCT images were acquired using the Spectralis HRA + OCT (Heidelberg Engineering Inc., Heidelberg, Germany). The posterior segment centered on the fovea was scanned by 8.8 mm × 7.3 mm at 240 μ intervals, at 8.8 images per second, with a resolution of 5 μm. SFCT on EDI-OCT images was defined as the vertical distance between the outer surface of the RPE to the choroidal-scleral interface at the fovea.[34]

Indocyanine green angiography images

ICGA was performed after an intravenous injection of 25 mg of indocyanine green (Santen Company Ltd., Osaka, Japan). Ultra-widefield ICGA images were captured using an ultra-wide-field imaging device (Optos California ultra-wide-field imaging device; Dunfermline, Scotland, UK). Sequential time-stamped images were obtained for each eye during transit and completion of choroidal filling. Images were digitally captured using the Optos V2 Vantage Review

Software and subsequently compressed into high-quality JPEG/TIFF files. Using dual FA/ICGA scoring system established by The Angiography Scoring for Uveitis Working Group,[35] ICGA signs were scored in a masked fashion by three ophthalmologists, and the averages were used.

Statistical analysis

Statistical analyses were performed using JMP pro version 15 (Business Unit of SAS, Cary, NC, USA). Changes in LogMAR, flare count, SFCT, ICGA score, and the daily dose of systemically administrated corticosteroids at baseline before the initiation of ADA treatment and at 6 months (M) after the treatment were analyzed by paired *t*-test (parametric data) and Wilcoxon's matched-pairs signed rank test (nonparametric data). Spearman's correlation coefficient test and multiple regression analysis were used to assess the correlation between LogMAR VA and flare counts, SFCT, and ICGA. $P > 0.05$ were considered statistically significant. The usage of immunosuppressors was analyzed by the Chi-square test.

Results

Demographic and general data

The mean age of VKH patients was 55.9 ± 14.4 years, and the male/female ratio was 26/24. The mean of LogMARVA was 0.37 ± 0.82, and BCVA <20/200 was 16%. The mean daily dose of systemic corticosteroids was 16.5 ± 12.7 mg, and 22 patients (44%) were under immunosuppressors. Multimodal images of a representative case of chronic recurrent VKH patients with SGF are shown in Figure 1.

Ocular findings at baseline and 6 months after adalimumab treatment in chronic recurrent Vogt-Koyanagi-Harada patients with sunset glow fundus

LogMARVA and BCVA at baseline and 6 M after the initiation of ADA treatment in chronic recurrent VKH patients with SGF are shown in Figure 2. The average of logMARVA at baseline of 0.37 ± 0.82 was significantly reduced to 0.12 ± 0.55 at 6 M after ADA treatment ($P = 0.0238$) [Figure 2a], and the proportion of BCVA <20/200 reduced from 16% to 5% and BCVA more than 20/20 increased from 57% to 68% [Figure 2b]. Figure 3 presents flare counts, SFCT, and ICGA scores of chronic recurrent VKH patients with SGF at baseline and 6 months after the initiation of ADA. Statistically significant improvements from 24.8 ± 43.1ph/ms to 13.1 ± 13.8 ph/ms were noted for flare counts ($P = 0.0239$), from 358 ± 212 μm to 313 ± 157 μm for SFCT ($P = 0.0464$), and from 8.14 ± 4.14 to 7.05 ± 5.68 for ICGA score ($P < 0.0001$).

Evolution of immunosuppressive treatments at baseline and 6 months after adalimumab treatment in chronic recurrent Vogt-Koyanagi-Harada patients with sunset glow fundus

Regarding treatments, the mean daily corticosteroid dose was significantly reduced from 16.5 ± 12.7 mg/day at baseline to 7.05 ± 5.68 mg/day at 6 months after the initiation of ADA ($P < 0.0001$) [Figure 4a]. Methotrexate (MTX) was additionally provided for 6 VKH patients after ADA treatment; however, CYA treated patients significantly decreased from 40% to 6%, and patients without immunosuppressors increased from 56% to 80%, which was also statistically significant ($P = 0.0005$) [Figure 4b].

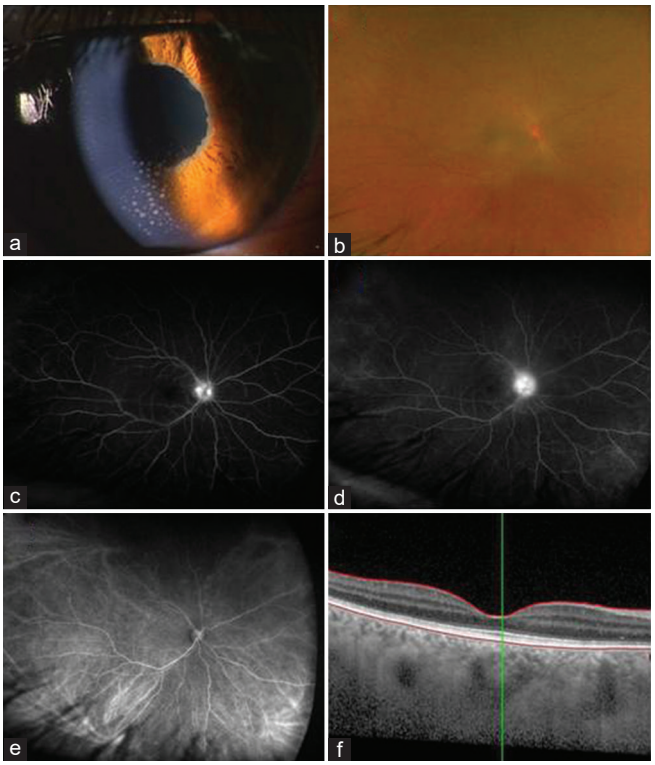

Figure 1: Multimodal imaging in chronic recurrent VKH patients with SGF. The anterior segment photograph (a), the fundus photographs (b), FA in the early phase (c) and the late phase (d), IA in the late phase (e), and the horizontal SD-OCT B scan passing through the fovea (f) in the right eye of anchronic recurrent VKH patients with SGF are shown. Mutton-fat keratic precipitates were observed from the center to the lower part of the cornea, and Koeppe's nodules are presented in the pupillary region (a). Yellow-white retinal lesions associated with SRD were absent (b), and punctate dye leakage at the early stage and the pooling at the late stage on FA were also absent (c and d). However, hyperfluorescence of the optic disc was evident from the early phase of FA (c and d). On ICGA, numerous HDDs and peripheral fuzzy vessels were observed (e). EDI-OCT images through the fovea exhibited choroid thickening but not SRD (Figure 1f). VKH: Vogt-Koyanagi-Harada, SGF: Sunset glow fundus, FA: Fluorescein angiography, SRD: subretinal detachment, HDDs: Hypofluorescent dark dots, EDI-OCT: Enhanced depth imaging optical coherence tomography

Association of LogMAR visual acuity with flare counts, subfoveal choroidal thickness, and indocyanine green angiography scores

Since VA of chronic recurrent VKH patients with SGF was significantly improved with a decrease of flare counts, SFCT, and ICGA scores by ADA treatment for 6 M, we examined the correlation of LogMAR VA with these ocular findings using both data before and 6M after ADA treatment. As shown in Figure 5, LogMAR VA in chronic recurrent VKH patients with

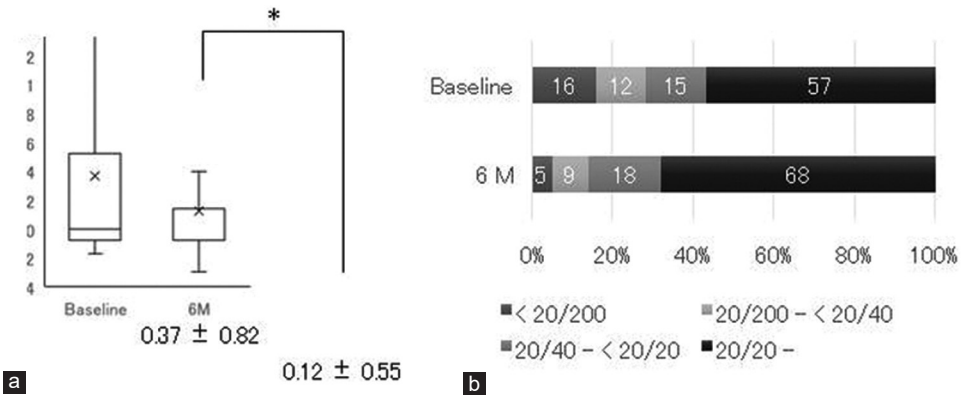

Figure 2: LogMAR visual acuity and BCVA at baseline and 6 months after ADA treatment in whole VKH patients. The box plots of LogMAR visual acuity (a) and percentage component bar graphs of BCVA (b) at baseline and 6 months after the initiation of ADA treatment in chronic recurrent VKH patients with SGF are shown. "X" is the average.* indicates $P < 0.05$. BCVA: Best corrected visual acuity, VKH: Vogt-Koyanagi-Harada

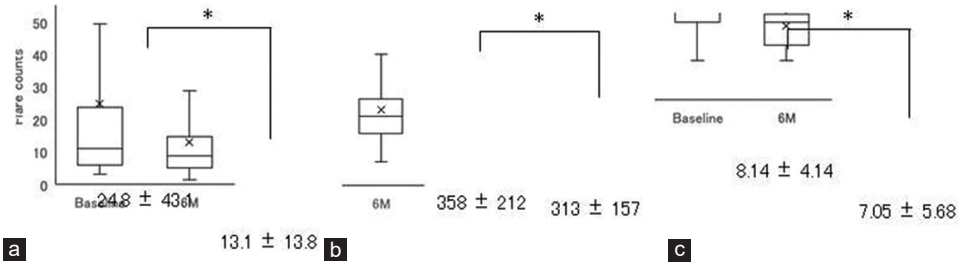

Figure 3: Ocular examination findings at baseline and 6 months after ADA treatment in whole VKH patients. Flare counts (a), SFCT (b), and ICGA scores (c) at baseline and 6 months after the initiation of ADA treatment in chronic recurrent VKH patients with SGF are shown by the box plots. "X" is the average. * indicates $P < 0.005$. SFCT: Subfoveal choroidal thickness, ADA: Adalimumab, ICGA: Indocyanine green angiography, VKH: Vogt-Koyanagi-Harada, SGF: Sunset glow fundus

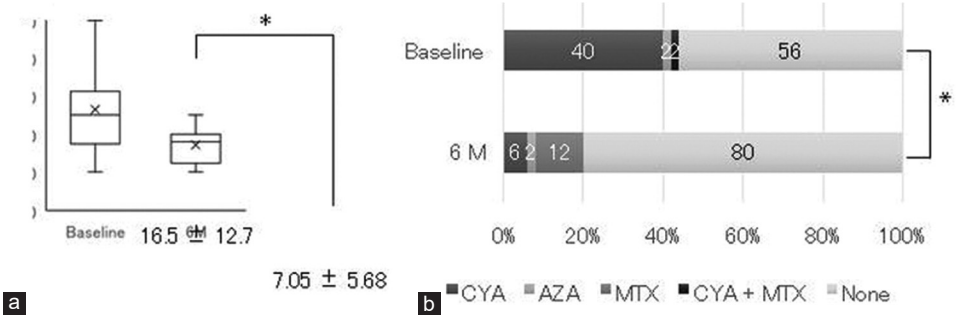

Figure 4: Corticosteroids and immunosuppressors at baseline and 6 months after ADA treatment in whole VKH patients. The box plots of corticosteroids (a) and percentage component bar graphs of immunosuppressants (b) at baseline and 6 months after the initiation of ADA treatment in whole VKH patients are shown. "X" is the average. * indicates $P < 0.005$. ADA: Adalimumab, VKH: Vogt-Koyanagi-Harada

SGF was significantly correlated with flare counts ($R_2 = 0.638$, $P < 0.0001$) and SFCT ($R_2 = 0.020$, $P < 0.05$), but not with ICGA scores ($R_2 = 1.036e\text{-}5$, $P = 0.976$). Subsequently, the association of LogMAR VA with flare counts, SFCT, and ICGA scores was investigated by multiple regression analysis [Table 1], and LogMAR VA was significantly related to flare counts but not to SFCT nor to ICGA scores.

Adverse events and continuation of adalimumab treatment

Adverse events and the continuation rate of ADA treatment are shown in Table 2. Adverse events were observed in seven (14%) patients, in which serious infection of reactivation of latent tuberculosis in 2 (4%) cases, psoriasis in 2 (4%) cases, and allergic reactions in 1 (2%) case were observed. ADA treatment was suspended in three (6%) patients, but was continued in 47 (94%) patients.

Discussion

The present study demonstrated that ADA treatment was effective for chronic recurrent VKH patients with SGF who inadequately responded to corticosteroids with or without immunosuppressors or were unable to continue the ongoing conventional immunosuppressive treatment due to the side

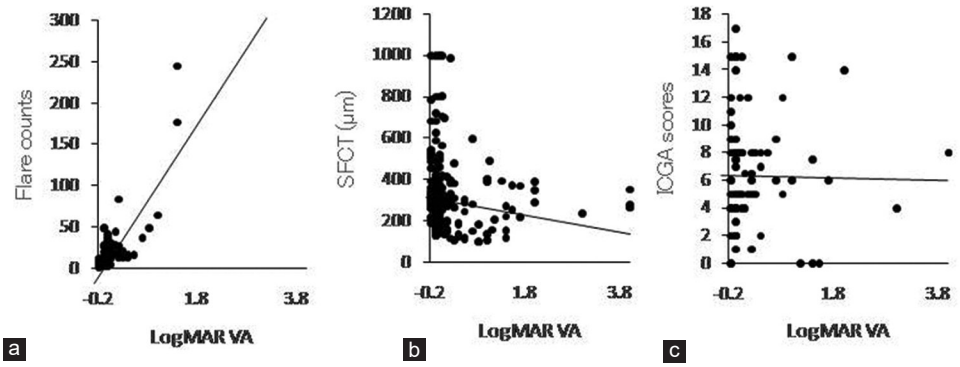

Figure 5: Association of LogMAR VA with ocular examination findings in chronic recurrent VKH patients with SGF. The correlation of LogMAR VA with flare counts (a), SFCT (b), or ICGA scores (c) was analyzed by Spearman''s correlation coefficient test. (a) y = 16.3 + 88.4x, R_2 = 0.638, $P < 0.0001$, (b) y = 345 + 37.8x, R_2 = 0.020, $P < 0.05$, and (c) y = 6.72 + 0.02x, R_2 = 1.036e-5, $P = 0.976$. SFCT: Subfoveal choroidal thickness, VKH: Vogt-Koyanagi-Harada, ICGA: Indocyanine green angiography

Table 1: Multiple regression analysis of LogMAR visual acuity with flare counts, subfoveal choroidal thickness, and indocyanine green angiography scores in chronic recurrent Vogt-Koyanagi-Harada patients with sunset glow fundus

LogMAR VA (adjusted R^2=0.5879, P<0.0001)	Estimate	*t*	*P*
Flare counts	0.006	7.93	<0.0001
SFCT	−8.16e-6	−0.06	0.9531
ICGA scores	−0.003	−0.50	0.6210

SFCT: Subfoveal choroidal thickness, ICGA: Indocyanine green angiography, VA: Visual acuity

Table 2: Adverse events and the continuation rate of adalimumab treatment

	VKH disease patients with SGF (n=50), n (%)
Adverse events	7 (14)
Serious infection	2 (4)
Allergic reactions	1 (2)
Psoriasis	2 (4)
Others	2 (4)
Continuation	47 (94)
Suspension	3 (6)

VKH: Vogt-Koyanagi-Harada, SGF: Sunset glow fundus

effects.

In the VISUAL I study, which was a randomized, double-masked, placebo-controlled clinical trial, the effects of ADA for noninfectious uveitis containing VKH patients were assessed in inducing and maintaining remission combined with corticosteroids,[19] and in the VISUAL II study, the corticosteroid-sparing effect with prevention of relapses of uveitis was investigated.[20] The results of both studies indicated that ADA treatment effectively decreased the ocular inflammation of active uveitis, and the achieved remission was maintained with corticosteroid-sparing effects. The Visual III study, an open-label prolonged study of the VISUAL I and II studies, implicated that the maintenance of the achieved remission was further increased by continuous ADA treatment.[36] Occasionally, ordinal clinical practice differs from a clinical trial conducted based on rigorous subject selection, uniformed treatment protocols, and adjusted endpoints. However, real-world clinical data also implied the efficacy and safety of ADA treatment for patients with noninfectious uveitis.[37]

Regarding ADA treatment for VKH disease, Couto *et al*. reported that in a case series of VKH patients with active ocular inflammation refractory to conventional therapy, ADA treatment resulted in the resolution of inflammation in 13 of 14 patients and reduced systemic corticosteroid doses from 20 mg to 4 mg.[15] We have retrospectively investigated 70 VKH patients who received ADA treatment for more than 6 months in a multicenter study.[27] As a result, SFCT, ICGA scores, and corticosteroid and cyclosporine doses were significantly reduced by ADA treatment at 6 months compared to baseline, and LogMAR VA and flare counts were also improved. In addition, ADA is useful for pediatric VKH patients in whom high-dose corticosteroid therapy has to be avoided because of growth impairment.[22-24] There are also other reports that sufficient remission of ocular inflammation was achieved and maintained in VKH patients after switching from infliximab to ADA,[16] and that a case of VKH disease with bullous central serous chorioretinopathy, which was induced by the side effect of systemic corticosteroid, was successfully treated by ADA.[21]

ADA treatment of chronic recurrent VKH patients with SGF for 6 M in our series significantly improved IogMAR VA and reduced flare scores, SFCT, ICGA scores, and mean daily corticosteroid dose. In order to identify factors related to LogMAR VA in chronic recurrent VKH patients with SGF, we performed correlation analysis and multiple regression analysis using both data before and 6M after ADA treatment. LogMAR VA was significantly correlated with flare counts and SFCT; however, multiple regression analysis identified only flare count as a factor related to LogMAR VA. An increase of flare counts indicates damage of blood-ocular barriers by the anterior inflammation.[38] Since chronic recurrent VKH disease presents more severe anterior inflammation than initial-onset

acute VKH disease,[9] flare counts are generally higher in patients with chronic recurrent VKH disease than those with initial-onset acute VKH disease.[39] Since opacification of intermediate translucent bodies directly affects VA, it was expected. On the other hand, as the ICGA score is the most sensitive parameter for assessing activity in chronic relapsing VKH disease, our results suggest that the intensity of choroidal inflammation does not necessarily correlate with VA.

SFCT was significantly diminished in chronic recurrent VKH patients with SGF after 6 months of ADA treatment compared to baseline values. Ormaecheaet al. showed SFCT in chronic VKH patients positively correlated with anterior segment inflammatory activity,[40] and it was also reported that anterior segment recurrence in VKH disease might occur concomitantly with subclinical choroidal inflammation.[41] However, anterior segment inflammation of recurrent VKH disease in these studies was only assessed using categorical value proposed by the SUN working group,[42] which is obviously not an objective numerical evaluation. We have previously evaluated underlying subclinical ocular inflammation in VKH patients with SGF by flare counts, SFCT, and ICGA scores, and found that flare counts were positively correlated with ICGA scores, but there was no association between SFCT and flare counts.[43] Furthermore, in the present study, SFCT in chronic recurrent VKH patients with SGF was not significantly correlated with the flare counts (data not shown).

Although ADA treatment significantly reduced the mean daily dose of oral corticosteroids and the number of patients receiving cyclosporine, VKH patients receiving MTX increased after ADA treatment. MTX was prescribed to prevent the production of neutralizing antibodies against ADA, not to suppress intraocular inflammation of chronic recurrent VKH disease.

Regarding severe adverse events, reactivation of latent tuberculosis was observed in 2 (4%) cases and psoriasis was in 2 (4%) cases. ADA treatment was suspended in 3 cases (6%). However, malignancy, inflammatory neurologic disease, opportunistic infections, or demyelinating disease were not seen in this study. The rates of adverse events and discontinuations due to adverse events in the present study were within the range of rates in other studies.[15,17-20]

The limitations of the present study include the retrospective design, inclusion of only Japanese participants, and the single-arm study without controls, and the fact that patients were at different stages of chronicity meaning diverse timing of ADA intervention.

In conclusions, remission of ocular inflammation was achieved and maintained by ADA treatment in chronic recurrent VKH patients with SGF who inadequately responded to conventional immunosuppressive therapy. ADA was well tolerated, with few serious adverse events.

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Conflicts of interest

There are no conflicts of interest.

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