Multimodal Analysis and Electroretinogram in VKH From Acute Onset - Part I

NCT03811366

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STUDY PROTOCOL

Prospective cohort study on VKH disease conducted from June 2011 through January 2017 at Uveitis Service, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, SP, BR. The local institutional review board approved the full protocol, which follows the tenets of the declaration of Helsinki (clinicaltrials NCT03811366).

The inclusion criteria consisted of: diagnosis of VKH disease in the acute phase according to the International Committee in 2001 [1]. The exclusion criteria were: less than a 24-month follow-up period and contraindication to corticosteroid therapy. Treatment protocol included a three-day course of intravenous methylprednisolone (1000 mg per day) followed by a high dose of oral prednisone (1.0 mg/kg/day) with a slow tapering with dose equal or less than 0.1mg/kg/day after 10 months. The prednisone dose was scheduled to be reduced in a 0.1 mg/kg-step ladder until it reaches 0.3 mg/kg (i.e., for an individual with 60 kg, dose would be 20 mg): from 1 to 0.8 mg/kg every two to three weeks; at 0.7 mg/kg for 4 weeks; at 0.6 mg/kg for two to three weeks; from 0.5 mg/kg every 4 weeks; from 0.3 to 0.15 mg/kg every 6 weeks; and 0.1 mg/kg, 0.075 mg/kg and 0.05 mg/kg for 8 weeks each. Oral corticosteroid dose increase was prescribed in case of persistent clinical inflammation signs in two steps and at least 0.5 mg/kg/d. For example, if a patient with 60 kg presents worsening of inflammatory signs while in use of 0.4 mg/kg/d, oral corticosteroid should be increased to 0.6 mg/kg/d. On the other hand, if a patient with 60 kg presented a clinical flare while using 0.2 mg/kg/d, the oral corticosteroid should be increased to at least 0.5 mg/kg/d. Subsequent tapering would be performed as previously scheduled. Additional non-steroidal immunosuppressive therapy (IMT) would be prescribed if the patient presented intolerance due to side effects (e.g., psychosis) or prednisone monotherapy-refractory inflammation. IMT use would be considered as an additional therapy if implemented for at least six months and if includes cyclosporine A, azathioprine, or mycophenolate mofetil.

Examinations were performed at inclusion, 1, 2, 4, 6 months (M), and, thereafter, every 3 months. Each visit included complete clinical and imaging examinations (e.g., fundus color photography, ICGA, fluorescein angiography – FA and EDI-OCT). ff-ERG was performed at inclusion; at 30 days and at 6 months intervals thereafter, using RETI-port system (Roland Consult; Electrophysiological Diagnostic Systems, Brandenburg, Germany). Fundus color photography was performed using the Topcon

TRC-50DX (Tokyo, Japan); FA, ICGA and EDI-OCT were performed using Spectralis® HRA+OCT (Heidelberg Engineering, Germany). Fundus findings were graded according to a previously described analytical framework [2]. The development of sunset glow fundus was classified as either present or absent based on the fundus color photography. Imaging examinations were read by two well-trained examiners. In case of instances of disagreement, the senior reader would classify the images and would be responsible for the final decision. The FA and ICGA reading charts were adapted from Tugal-Tutkun et al [3]. Dark dots (DD) were evaluated based on a semi-quantitative score for the posterior pole and each quadrant: sparse and/or faint and numerous and/or pronounced. The total score varies from 0 to 8. Fluctuation was defined as a change in DD quantity (e.g., sparse to numerous or vice versa) according to the Tugal-Tutkun et al score and whether the DD in the posterior pole or in each quadrant [3]. Objectively, DD fluctuation was defined as a final score variation ≥ 0.5 between two different points in time. ff-ERG recordings were performed in accordance with the International Society for Clinical Electrophysiology of Vision guidelines with the RETI-port system (Roland Consult) using ERG-jet electrodes (Universe SA, La Chaux-deFons, Switzerland) [4]. Scotopic ERG responses were recorded after a period of 20 minutes of dark adaptation, and photopic ERG responses were recorded after 10 minutes of light adaptation. The recording sequence was scotopic rod response, scotopic cone–rod combined response, scotopic oscillatory potentials, photopic cone response, and 30-Hz flicker cone response. The normal value limits for each specific ERG response were established at 95% confidence intervals. Amplitude and implicit time of a and b wave of eight averaged stimulus response for each phase were analyzed, and the results were compared with a normative database. The worsening of the ERG parameters was defined as value reduction > 30% in any scotopic ERG parameter, which needed to be confirmed in two consecutive examinations [5]. ff-ERG scotopic parameters obtained at 12 and 24 months were compared; all included eyes were grouped based on the worsening or stabilization of the scotopic parameters from 12th to 24th month.

After the acute inflammatory phase (six months following disease onset), disease activity was systematically evaluated based on both clinical and subclinical signs. Specifically, clinical signs included anterior chamber cells (ACC) of at least 1+ cells, exudative retinal detachment, and macular edema confirmed on FA and/or OCT. Visual acuity measurement with a Snellen chart was converted to LogMAR values. Subclinical

signs are those detected exclusively in posterior segment imaging (PSI) and included optic disc leakage/hyperfluorescence (ODH) and/or perivascular leakage on FA; hypofluorescent DD on ICGA; and, increase of at least 30% in subfoveal choroidal thickness (CT) in two consecutive EDI-OCT examinations. Perivascular leakage was observed as an increase in hyperfluorescence around retinal vasculature over time on FA exam at midperiphery. Isolated subclinical signs of activity did not infer change in treatment schedule, whereas clinical signs led to either an increase in a daily oral prednisone dosage of 0.2 mg/kg (up to at least 0.5 mg/kg/day) or the introduction of non-steroidal IMT (i.e., azathioprine, cyclosporine, or mycophenolate mofetil). Any intolerance to corticosteroid also determined a switch in treatment to non-steroidal IMT. Based on the predefined protocol, the term "flare" was used to describe the appearance or worsening of inflammatory signs observed at least sixth months after disease onset. During the 24-month follow-up period, the presence of ocular complications (i.e., cataract [6], ocular hypertension/glaucoma [7,8], choroidal neovascularization (CNV) [9], or SGF) was recorded. Cataract was defined as any lens opacification greater than nuclear or cortical 2+/4 or subcapsular 1+/4 [6]. Ocular hypertension was defined as an intraocular pressure (IOP) above 21mmHg [7,8]. The CNV membrane was diagnosed when increasingly localized hyperfluorescence at the posterior pole is detected on FA or a hyperreflective subretinal lesion associated with sub or intraretinal fluid on OCT.

The main outcomes measures included clinical and subclinical flares, presence of sunset glow fundus, and ff-ERG results from 12 to 24 months of follow-up.

STATISTICAL ANALYSIS PLAN WITH RESULTS INFORMATION

Twelve patients (24 eyes, 10 female) with acute VKH disease were included in the study. For descriptive data analysis, medians and ranges were calculated. **Table 1** summarizes the data regarding clinical and subclinical signs of inflammation, complications and ff-ERG results during the 24-month follow-up.

Table 1 Inflammatory signs and ocular complications observed during the 24-month follow-up, excluding the initial 6 months, and electroretinogram results at the 24 months in patients with Vogt-Koyanagi-Harada disease

Case	Eye	Cells in anterior chamber	PSIIS			Complications				ERG	
			Dark dots increase (n° of episodes)	Perivascular leakage	CT increase	Cataract	Ocular hypertension	CNV membrane	SGF	Subnormal* at 24 months	Variation between 12 and 24 m
1	RE	Yes	2	No	No	No	Yes	No	No	No	Stable
	LE	Yes	1	No	No	No	Yes	No	No	No	Stable
2	RE	No	1	No	No	No	Yes	Yes	Yes	Yes	Worsening
	LE	No	1	Yes	No	No	Yes	No	Yes	Yes	Worsening
3	RE	No	2	No	Yes	No	No	No	No	Yes	Worsening
	LE	No	2	No	Yes	No	No	No	No	Yes	Worsening
4	RE	No	3	Yes	No	No	Yes	No	No	Yes	Stable
	LE	No	2	Yes	Yes	No	Yes	No	No	No	Worsening
5	RE	Yes	1	No	Yes	Yes	Yes	No	No	No	Stable
	LE	Yes	1	No	Yes	Yes	Yes	No	No	No	Stable
6	RE	No	0	Yes	Yes	No	Yes	No	No	Yes	Worsening
	LE	No	0	Yes	No	No	Yes	No	No	Yes	Worsening
7	RE	Yes	1	Yes	Yes	No	No	No	Yes	Yes	Stable
	LE	Yes	3	Yes	Yes	No	No	No	Yes	Yes	Stable
8	RE	No	1	Yes	No	No	No	No	Yes	Yes	Stable
	LE	No	2	Yes	No	No	No	Yes	Yes	Yes	Stable
9	RE	Yes	1	Yes	No	No	No	No	Yes	Yes	Stable
	LE	Yes	1	Yes	No	No	No	Yes	Yes	Yes	Stable
10	RE	No	1	Yes	Yes	Yes	Yes	No	No	No	Stable
	LE	No	3	Yes	Yes	No	Yes	No	No	No	Stable
11	RE	No	1	No	Yes	Yes	No	No	Yes	Yes	Stable
	LE	No	1	No	Yes	Yes	No	No	Yes	Yes	Stable
12	RE	No	1	No	No	No	No	No	No	No	Stable
	LE	No	1	No	No	No	No	No	No	No	Stable

PSIIS, posterior segment imaging inflammatory sign observed on indocyanine green angiography, on fluorescein angiography and on enhanced depth imaging optical coherence tomography; CT, choroidal thickness; CNV, choroidal neovascular membrane; SGF, sunset glow fundus; ERG, electroretinography

*Subnormal ERG means at least one scotopic parameter below normal range when compared to control group

For the comparison of qualitative and quantitative data between the stable ERG and worsening ERG groups, the Fisher exact test and Mann Whitney test, respectively, was used (**Tables 2 and 3**). Furthermore, Kappa statistics was used to test interrater reliability between subnormal ERG and SGF. P values ≤ 0.05 were considered statistically significant. Generalized estimated equations (GEE) were used for analyzing binary ocular data. (**Tables 2 and 3**) Data analysis and statistical tests were conducted using SPSS 20.0 (SPSS Science, Chicago, IL, USA).

Table 2 Electroretinogram results at 12 and 24 months (median value) and variation between 24 and 12 months in patients with Vogt-Koyanagi-Harada disease and controls

Parameters[a]	Controls ($n = 61$ eyes)	Patients				ERG-based groups						
		($n = 24$ eyes)				Stable ($n = 17$ eyes)			Worsening ($n = 7$ eyes)			
		T12	T24	T24-T12[b]	p[c]	T12	T24	T24-T12[b]	T12	T24	T24-T12[b]	p[d]
Scotopic												
[b]Amplitude (μV)	211 (114–366)	201 (104–352)	189 (130–380)	8 %	0.504	192 (104–352)	210 (130–380)	9.5 %	231 (112–300)	161 (134–183)	− 32.9 %	0.006
[b]Latency (ms)	77 (70–86)	89 (78–100)	89 (75–99)	− 0.4 %	< 0.001	90 (78–100)	89 (75–99)	− 0.6 %	87 (81–92)	148 (120–262)	2.3 %	0.319
Maximum scotopic												
[a]Amplitude (μV)	300 (211–440)	210 (134–336)	189 (120–317)	− 1.5 %	< 0.001	203 (134–336)	224 (166–317)	7 %	215 (157–330)	148 (120–262)	− 21.4 %	< 0.001
[a]Latency (ms)	22 (18–23)	23 (19–25)	23 (20–55)	− 0.6 %	0.008	23 (22–25)	23 (22–55)	− 1.3 %	23 (19–24)	24 (20–54)	5.2 %	0.295
[b]Amplitude (μV)	510 (348–789)	508 (328–728)	484 (336–769)	− 1.4 %	0.164	507 (328–728)	528 (355–769)	2.8 %	546 (398–597)	404 (336–540)	− 10.8 %	0.001
[b]Latency (ms)	44 (36–50)	50 (44–62)	50 (41–55)	− 2.3 %	< 0.001	50 (44–62)	50 (46–55)	− 1.3 %	49 (45–50)	46 (41–54)	− 3.3 %	< 0.001
Oscillatory potential (μV)	121 (92–228)	92 (48–272)	114 (35–259)	0.7 %	0.215	95 (48–272)	135 (46–259)	5.9 %	88 (71–119)	55 (35–130)	− 47.1 %	0.168
Photopic												
[a]Amplitude (μV)	50 (34–89)	42 (23–63)	43 (23–66)	− 1 %	0.004	42 (23–60)	44 (23–66)	0 %	33 (25–63)	33 (24–52)	− 5 %	0.328
[a]Latency (ms)	15 (14–17)	16 (14–17)	16 (14–17)	− 2.2 %	0.005	16 (15–17)	16 (14–17)	− 2.5 %	16 (14–17)	16 (14–17)	3.7 %	0.723
[b]Amplitude (μV)	227 (106–367)	202 (87–312)	186 (111–345)	− 1.4 %	0.025	190 (113–312)	209 (147–345)	2.4 %	218 (87–236)	176 (111–190)	− 13.6 %	0.139
[b]Latency (ms)	31 (27–34)	31 (29–35)	31 (29–33)	− 2.6 %	0.263	31 (29–35)	30 (29–33)	− 1.8 %	32 (31–33)	31 (29–32)	− 2.8 %	0.628
Flicker 30 Hz	68 (42–122)	52 (24–89)	54 (29–85)	0.3 %	< 0.001	53 (32–89)	55 (37–85)	6.2 %	52 (24–81)	36 (29–67)	− 6.9 %	0.189

[a] ERG measures represented as median; ERG: electroretinography, Mann-Whitney test between ERG-based groups; [b] difference, in percentage, between values observed at 24 and 12 months was calculated for each patient and the median value is here represented; [c] p value comparing controls × patients at 24 months—generalized estimated equation with normal distribution and logarithmic link function, supposing an interchangeable correlation matrix between the eyes; [d] p value comparing T24—12 months between stable and worsening ff-ERG groups—generalized estimated equation with normal distribution and logarithmic link function, supposing an interchangeable correlation matrix between the eyes

Table 3 Electroretinogram-based groups of patients with Vogt-Koyanagi-Harada disease and their clinical characteristics

	ERG-stable group	ERG-worsening group	*p*
N (eyes)	17	7	
Age, years, median (range)	32 (15–42)	22 (21–67)	0.864[a]
Interval to treatment start, days, median (range)	21 (3–51)	17 (7–33)	0.727[a]
Visual acuity at M1(logMAR), median (range)	0.3 (0–2)	0.1 (0–0.7)	0.433[b]
Choroidal thickness at M1, μm, median (range)	545 (308–904)	635 (303–911)	*0.001*[c]
Inflammatory signs, eyes (%)			
Anterior chamber cells fluctuation	8 (47.1)	0 (0)	0.054[d]
Choroidal thickness fluctuation, eyes (%)	8 (47.1)	4 (57.1)	0.022[e]
Dark dots fluctuation[∞]			
None	0 (0)	2 (28.6)	0.478[f]
One	12 (70.6)	2 (28.6)	
Two	2 (11.8)	3 (42.8)	
Three	3(17.6)	0 (0)	
Perivascular leakage	9 (52.9)	4 (57.1)	0.936[e]
Ocular complications, eyes (%)			
Cataract	5 (29.4)	0 (0)	0.272[d]
Ocular hypertension	7 (41.2)	5 (71.4)	0.983[e]
Sunset glow fundus	8 (47.1)	2 (28.6)	0.988[e]
Neovascularization	2 (11.8)	1 (14.3)	0.853[e]
Fibrosis	4 (23.5)	2 (28.6)	0.846[e]
Treatment, patients (%)			
Additional NS immunosuppression	5 (55.6)	1 (33.3)	> 0.999[d]
Prednisone increment**	6 (66.7)	2 (66.7)	> 0.999[d]

[a] Mann-Whitney; [b] generalized estimated equation with normal distribution and logarithmic link function, supposing an interchangeable correlation matrix between the eyes; [c] generalized estimated equation with normal distribution and identity link function, supposing an interchangeable correlation matrix between the eyes; [d] Fisher exact test; [e] generalized estimated equation with binomial distribution and logit link function, supposing an interchangeable correlation matrix between the eyes;; [f] generalized estimated equation with Poisson distribution and identity link function supposing an interchangeable correlation matrix between the eyes; [∞] increase in the number of DD by region, whether in the posterior pole or in each quadrant, followed by a diminishment. Objectively was defined as a variation in the final score between two different points in time ≥ 0.5(Tugal-Tutkun et al., 2010). NS, non-steroidal; **two patients that received increment in prednisone dose presented one eye in stable and one eye in worsening groups

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