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Early Versus late Immunomodulatory Therapy in Vogt-Koyanagi-Harada Disease

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Abstract

Purpose: To evaluate early versus late immunomodulatory therapy (IMT) for patients following initial diagnosis of Vogt-Koyanagi-Harada (VKH) disease.

Methods: Retrospective review including all VKH patients seen 5/1/2014 to 4/1/2016 at LAC+USC. Early IMT was defined as starting an immunomodulatory agent within 3 months of corticosteroid initiation.

Results: Twenty-seven patients were included, of whom 15 received early IMT and 8 received late IMT. Early IMT patients trended toward greater improvement in vision compared to late IMT (logMAR 0.59 vs. 0.11; p=0.14) with no differences in ocular complications including ocular hypertension (p=0.53) and cataract (p=1.0). Patients receiving early IMT averaged 0.93 recurrences versus 2.13 recurrences for late IMT (p=0.092). Of patients successfully taper off oral corticosteroids, the early IMT group was tapered in an average of 8.3 months versus 19.8 months for late IMT (p=0.0019).

Conclusions: Early IMT in VKH may allow for shorter duration of corticosteroids with similar visual outcomes, ocular complications, and disease recurrences.

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Introduction

Vogt-Koyanagi-Harad disease (VKH) is a bilateral panuveitis that primarily affects pigmented ethnicities including Hispanic, Asian, and Native Americans.[1] Also known as uveomeningitis syndrome, VKH is an idiopathic inflammatory disease characterized by chronic, diffuse, granulomatous panuveitis frequently associated with neurological, auditory, and integumentary manifestations.[2] While the exact cause of the disease remains unknown, T-lymphocyte-mediate autoimmunity against tyrosinase peptides of melanocytes is present.[3,4] A genetic predisposition has been shown with an association between VKH and HLA-DR1 and HLA-DR4 in Hispanics as well as several HLA specificities in Asians.[5-7] While the disease is more prevalent in Asia, VKH accounts for between 1% to 4% of uveitis referrals within the United States.[8,9]

Vogt-Koyanagi-Harada disease generally presents in four phases: 1) a prodromal phase with auditory and neurologic symptoms 2) an acute uveitic phase, which may include diffuse choroiditis, exudative retinal detachment, and intraocular inflammation 3) a chronic phase, consisting of variable depigmentation of the fundus and limbus in addition to vitiligo, poliosis, and alopecia and 4) a chronic-recurrent phase with iridocyclitis, which may be chronic, recurrent or both. [10] The majority of people treated for VKH are prescribed high dose corticosteroids with a gradual taper and often require immunomodulatory therapy (IMT) such as methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, and occasionally, cyclophosphamide.[11] The purpose of this study was to evaluate the clinical course and outcomes in patients following initial diagnosis of VKH treated with early versus late immunomodulatory therapy.

Methods

A retrospective chart review was performed of all patients who received a first-time diagnosis of VKH at Los Angeles County + USC Medical Center seen between May 1, 2014 and April 1, 2016. The diagnosis of VKH was based on features typically present in the disease with the exclusion of other causes of uveitis by history, examination, and ancillary testing.[10] In order to capture the entire clinical course from first diagnosis of the disease, patients were excluded if they had been treated for VKH at an outside institution beginning more than one month prior to evaluation in our clinic.

Clinical charts were reviewed to collect patients' age, gender, ethnicity, visual acuity at each visit, clinical signs, treatment received, complications, and recurrences. Early IMT was defined as beginning any immunomodulatory therapy (mycophenolate mofetil, methotrexate, cyclosporine, etc.) within 3 months of starting oral corticosteroid treatment while a patient was categorized as late IMT if they began IMT more than 3 months following steroid initiation. Patients that were treated with corticosteroids (1 to 2 mg/Kg body weight) alone were considered as a separate category. When a patient was prescribed 10mg or less of daily oral prednisone, a patient was considered to have achieved a

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successful corticosteroid taper.

A recurrence of VKH was considered to have occurred if signs of anterior or posterior inflammation were present. Change in visual acuity was measured at first and last clinical visit. Snellen visual acuity was converted to logMAR equivalents with counting fingers corresponding to 1.98 and hand motions as 2.28. A visually significant cataract was considered to have developed if a lens was noted to have ≥3+ nuclear sclerosis, central posterior subcapsular cataract or had undergone cataract extraction on final visit. Patients with visually significant cataracts or intraocular lenses present at first visit were excluded from evaluation of cataract development. Ocular hypertension was considered present if the patient was started on intraocular pressure lowering medication or received incisional surgery at any time during the clinical course.

Statistical analysis included Fisher's exact test, chi-squared analysis, student t-test, and Wilcoxon rank sum analysis were performed using Stata version 14.2 (StataCorp, College Station, Texas).

Results

A total of 27 patients first diagnosed with VKH were identified over the period of interest and were included in our study. Demographic details are displayed in Table 1. Fifteen patients received early IMT while 8 patients received late IMT. Four patients were treated with corticosteroids alone.

Overall, the average age at diagnosis was 35.0 years and a majority of patients (63.0%) were female. Regarding ethnicity, one patient was Asian while 26 patients were Hispanic. The average length of follow-up was 39.2 months and 81.5% of patients had at least one year of follow-up. Average logMAR visual acuity at first presentation was 1.08 (approximately 20/250 Snellen equivalent). On first presentation, the majority of patients (70.4%) had acute VKH while 29.6% of patients had signs of chronic VKH. No significant difference was found in any of the above-mentioned variables when comparing patients who received early vs. late IMT.

Of the 15 patients receiving early IMT, 12 patients started IMT at the same time that corticosteroids were initially prescribed while 3 patients started IMT between 1 and 2 months following initiation of steroids. Patients in the late IMT group started IMT between 4 and 12 months following steroid initiation. Immunomodulatory agents used included mycophenolate mofetil, cyclosporine, azathioprine, methotrexate, infliximab, and adalimumab.

Clinical outcomes are summarized in Table 2. The majority of patients (59.3%) achieved best corrected visual acuity of 20/40 or better at the final clinic visit. The early IMT group trended toward better final logMAR visual acuity (0.55 vs. 0.92) and better change in logMAR visual acuity (0.58 vs. 0.11) compared to the late IMT group, although neither difference reached statistical significance (p=0.17 and p=0.14, respectively). Overall, 59.3% of patients were able to decrease oral prednisone to 10mg or less daily with no statistical difference between the early and late IMT groups. For the patients who were able to successfully taper off steroids, the time to achieve the steroid taper

Table 1: Characteristics of patients with Vogt-Koyanagi-Harada disease

	Overall	Early immunomodulatory therapy	Late immunomodulatory therapy	p-value
Patients, n (%)	27	15 (55.6%)	8 (29.6%)	
Female, n (%)	17 (63.0%)	10 (66.7%)	3 (37.5%)	0.11
Age, years (range)	35.0 (10.4 – 65.2)	34.4 (10.4 – 57.5)	36.8 (24.2 – 48.7)	0.53
Asian ethnicity, n (%)	1 (3.7%)	1 (6.7%)	0	1.00
Hispanic ethnicity, n (%)	26 (96.3%)	14 (93.3%)	8 (100%)	1.00
Length of follow-up, months (range)	39.2 (2.5 – 100.6)	43.0 (2.5-100.6)	34.3 (5.1-74.9)	0.47
Patients with 1+ year follow-up	22 (81.5%)	12 (80.0%)	7 (87.5%)	1.00
Visual acuity at first visit, logMAR (range)	1.08 (0-2.28)	1.12 (0.2-2.28)	1.03 (0-2.28)	0.44
Early phase VKH, n (%)	19 (70.4%)	10 (66.7%)	5 (62.5%)	1.0
Late phase VKH, n (%)	8 (29.6%)	5 (33.3%)	3 (37.5%)	1.0

Table 2: Outcomes of patients with Vogt-Koyanagi-Harada disease

	Total Population (54 eyes)	Early immunomodulatory therapy (30 eyes)	Late immunomodulatory therapy (16 eyes)	p-value
Eyes with visual acuity ≥ 20/40 at final visit	32/54 (59.3%)	18/30 (60.0%)	7/16 (43.8%)	0.53
Average visual acuity at final visit, logMAR	0.63	0.55	0.92	0.17
Change in visual acuity, logMAR	0.45	0.58	0.11	0.14
Time to achieve steroid taper, months	12.9	8.3	19.8	0.0019
Patients achieving steroid taper	16/27 (59.3%)	7/15 (46.7%)	6/8 (75.0%)	0.38
Recurrences, avg	1.30	0.93	2.13	0.092

was significantly shorter for the early IMT group compared to the late IMT group. Patients receiving early IMT tapered off oral prednisone in an average of 8.3 months while patients treated with late IMT tapered off steroids in an average of 19.8 months (p=0.0019).

Complications are summarized in Table 3. The average number of recurrences was trended lower in the early IMT group (0.93) compared to the late IMT group (2.13) although this did not reach statistical significance (0.092). In terms of complications, no significant differences were found between the early vs. late IMT groups. Overall, 38.1% of eyes developed visually significant cataracts and 46.3% of eyes developed glaucoma. Fundus depigmentation and nummular lesions developed in approximately half of all eyes (58.0% and 46.0%, respectively). Subretinal fibrosis developed in 6 eyes (11.1%) and choroidal neovascularization developed in 1 eye (1.9%).

Discussion

It is generally agreed that Vogt-Koyanagi-Harada disease requires systemic treatment. Early studies reported that patients with VKH receiving systemic corticosteroids achieved superior outcomes compared to patients receiving no systemic treatment.[12] Subsequent evaluations compared VKH patients receiving intravenous versus oral corticosteroids and found no significance differences in visual outcomes or complications.[13] As our armamentarium of immunomodulatory therapies has increased, our options to treat systemic uveitis have improved. However, the exact role and timing of IMT in VKH is still being elucidated.

Some physicians have elected to use immunomodulatory therapy alone as first line treatment for VKH and have reported similar visual outcomes compared to patients treated with corticosteroids alone.[14] However, given the limitations of previous reports, including small numbers and lack of prospective design, we have expressed caution towards using IMT as first line therapy for VKH.[11] We continue

Table 3: Outcomes of patients with Vogt-Koyanagi-Harada disease

	Total Population (54 eyes)	Early immunomodulatory therapy (30 eyes)	Late immunomodulatory therapy (16 eyes)	p-value
Visually significant cataract	16/42 (38.1%)	10/22 (45.5%)	6/14 (42.9%)	1.00
Ocular hypertension	25/54 (46.3%)	18/30 (60.0%)	7/16 (43.8%)	0.53
Ocular hypertension requiring incisional surgery	17/54 (31.5%)	14/30 (46.7%)	3/16 (18.8%)	0.11
Fundus depigmentation	29/50 (58.0%)	20/30 (66.7%)	7/12 (58.3%)	0.73
Nummular lesions	23/50 (46.0%)	14/30 (46.7%)	7/12 (58.3%)	0.74
Subretinal fibrosis	6/50 (12.0%)	4/30 (13.3%)	1/12 (8.3%)	1.00
Choroidal neovascular membrane	1/50 (2.0%)	0/30 (0%)	1/12 (8.3%)	0.29

to view first line therapy for acute VKH to consist of high-dose systemic corticosteroids with the possible addition of immunomodulatory therapy. With improved efficacy and safety of IMT as well as the chronic nature of VKH in the majority of patients, we often elect to begin IMT early in the disease course. This current study compared patients treated with early IMT versus late IMT for VKH. We found similar outcomes of visual acuity and complications between the groups as well as an association between early IMT and shorter duration of corticosteroid use (>10 mg) for some patients.

Overall, the majority of our patients achieved final visual acuity of 20/40 or better, which is similar to previous reports.[1,15,16] In our study, the overall average logMAR visual acuity improved 0.45, representing an improvement from approximately 20/250 to 20/80 Snellen visual acuity. We found that patients in the early IMT group had better final visual acuity (approximate Snellen equivalent 20/70 vs. 20/160) and greater improvement in visual acuity (logMAR 0.58 vs. 0.11) compared to the late IMT group although these differences did not reach statistical significance.

In terms of common complications, previous studies of VKH have reported glaucoma or ocular hypertension to occur in 6-45% of eyes and cataracts to develop in 11-42% of eyes.[1,16,17] In our study, ocular hypertension was the most common complication occurring in 46.5% of patients, which is at the high range of previous estimates. Previous evaluations of patients with VKH have shown that the development of complications is directly associated with increased follow-up time.[16] We hypothesize that our relatively high rate of ocular hypertension may be due to the long average follow-up of our patients (39.2 months) and that we defined ocular hypertension as uncontrolled IOP requiring intervention at any visit over the entire clinical course. Visually significant cataract occurred in just over one third of our patients, similar to prior studies. Subretinal fibrosis developed in approximately 10% of our patients similar to other reports ranging from 2.5-12% of cases.[1] Choroidal neovascularization was uncommon in our study occurring in only one eye. We found no differences in any ocular complications between the early and late IMT groups.

Corticosteroid taper in VKH is generally quite slow in order to avoid disease recurrences. Even with a prolonged taper, patients frequently have acute recurrences requiring a subsequent increase in corticosteroid therapy. We found that early IMT might allow for faster taper of corticosteroids without an increase in disease recurrence or inferior outcomes. Of the patients who were able to achieve a corticosteroid taper below 10mg oral prednisone daily, the early IMT group achieved a taper in 8.3 months compared to 19.8 months in the late IMT group, which was highly statistically significant. Furthermore, we found no increased risk of recurrences in the early IMT group. In fact, recurrences were lower in the early group, averaging 0.93 recurrences compared to 2.13 recurrences in the late IMT group, although this did not reach statistical significance. However, it should be

noted that overall only 60% of patients in this study achieved a steroid taper and we found no significant difference in the proportion of patients successfully tapered in the early vs. late IMT groups. In short, early IMT patients were no more likely to achieve a steroid taper but of those who successfully tapered, the length of corticosteroid treatment was shorter.

Corticosteroids are frequently poorly tolerated by patients, particularly at high doses or for prolonged periods of time, as treatment of VKH requires. Adverse effects such as weigh gain, skin thinning, sleep disturbances and neuropsychiatric disorders are common. Osteoporosis and increased risk of infection can result in life threatening complications. Adverse effects for steroids appear to be both dose and duration dependent and are estimated to occur in approximately 1 in 5 patients.[18,19] Each immunomodulatory therapy agent has a side effect profile which may include gastrointestinal disturbance in up to 30% of patients as well as myelosuppression, leukopenia, thrombocyto-penia, elevated liver enzymes and increased infection risk.[20] Both corticosteroids and immunomodulation are instrumental in managing ocular inflammatory disease but the possibility for adverse effects must be monitored for every patient.

Strengths of this study include the long-term follow-up and exclusion of previously treated patients. Only patients with a new diagnosis of VKH prior to treatment were included in order to fully capture the disease course. Limitations of our study include the retrospective design and the small number of patients, which can limit statistical significance of several of these variables due to inadequate power. As there is no grading scale for severity of VKH, we were unable to compare severity between the two groups. Previous studies have reported that initial visual acuity is often the best predictor of final visual outcome[16,21] and we did find that visual acuity was not significantly different between the groups at first visit. It is possible that immunomodulatory therapy may have been chosen earlier in patients with more severe disease. However, if this were the case, we might expect to see an increased rate of complications, such as choroidal neovascularization or subretinal fibrosis but we found no difference in complication rates. Finally, the timing of initiation of late IMT varied greatly between patients, which may make definitive conclusions difficult.

While corticosteroids were only tapered when a patient's inflammation was controlled, we did not directly evaluate the speed of resolution of the inflammation. By analyzing visual acuity at only the first and last clinical visits, we do not capture the effect of the treatment at intermediate time points. Disease complications were limited to ocular findings as systemic complications have been shown to be less common in Hispanic patients.[22] While the majority of patients at our institution were treated with IMT at some point during their disease, four patients were treated with corticosteroids alone. While we included this group in our overall tabulations, we did not do a subgroup analysis given the small number of individuals. Our study does not address when patients

may be treated with corticosteroids alone or whether outcomes differ compared to patients treated with IMT.

In summary, we found that patients treated with both early and late IMT for VKH generally do well as most patients achieve visual acuity of 20/40 or better. Ocular complications were similar between the groups and early IMT therapy was associated with better visual acuity outcomes although this finding was not significant. Early IMT may be associated with shorter duration of corticosteroid use with no difference in recurrence rates although further research is needed to fully assess the role and timing of immunomodulation in VKH.

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