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# The outcomes of mycophenolate mofetil therapy combined with systemic corticosteroids in acute uveitis associated with Vogt–Koyanagi–Harada disease

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**ABSTRACT.**

***Purpose:*** **To study the effectiveness of mycophenolate mofetil (MMF) as first-line therapy combined with systemic corticosteroids in acute uveitis associated with Vogt–Koyanagi–Harada (VKH) disease. The outcomes in this group were compared with those of another group of patients with VKH disease who were treated with corticosteroid monotherapy or with delayed addition of immunomodulatory therapy.**

***Methods:*** **This prospective study included 19 patients (38 eyes) diagnosed with acute uveitis associated with VKH disease.**

***Results:*** **The mean follow-up period was 27.0 ± 11.1 months (range 16–54 months). Corticosteroid-sparing effect was achieved in all patients. The mean interval between starting treatment and tapering prednisone to 10 mg or less daily was 5.1 ± 1.2 months (range 3–7 months). Ten (53%) patients discontinued treatment without relapse of inflammation. The mean time observed of treatment was 17.3 ± 11.9 months (range 3–41.5 months). Visual acuity of 20/20 was achieved by 38% of the eyes in the corticosteroid group and by 74% in the corticosteroid + MMF group ($p < 0.001$). Recurrent inflammation of ≥3 times was reduced significantly ($p = 0.0383$) in the corticosteroid + MMF group (3%) as compared to corticosteroid group (18%). Development of all complications was significantly higher in the corticosteroid group (43%) compared with the corticosteroid + MMF group (8%) ($p < 0.001$). None of the eyes in the corticosteroid + MMF group developed 'sunset glow fundus'.**

***Conclusions:*** **Addition of MMF as first-line therapy to corticosteroids in patients with acute uveitis associated with VKH disease leads to significant reduction in recurrences of uveitis and development of late complications and significantly improves visual outcome.**

**Key words:** complications – immunomodulatory therapy – mycophenolate mofetil – recurrence – Vogt–Koyanagi–Harada disease

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## Introduction

Vogt–Koyanagi–Harada (VKH) disease is a chronic, bilateral, granulomatous panuveitis and exudative retinal detachment associated with poliosis, vitiligo, alopecia, and central nervous system and auditory signs. The prevalence of the disease varies among different populations of the world, and it commonly affects pigmented races and people of certain genetic predispositions (Moorthy et al. 1995). HLA-DR4 and HLA-$DRW_{53}$, with the most significant risk allele being HLA-DRB1*0405, have been proven to be genetically associated with VKH disease (Fang & Yang 2008). The exact cause of VKH disease remains unknown, but evidence suggests that it involves a T-lymphocyte-mediated autoimmune process directed against one or more antigens found on or associated with melanocytes. Several studies demonstrated that tyrosinase family proteins are the antigens specific to VKH disease (Yamaki et al. 2000a,b; Gocho et al. 2001) and that VKH disease is characterized by an immune response mediated by T helper (Th)1 and Th17 cells (Abu El-Asrar et al. 2011). Vogt–Koyanagi–Harada disease is one of the most common uveitis entities in Saudi Arabia (Al-Mezaine et al. 2010), and the

visual prognosis is generally good with prompt diagnosis and appropriate immunosuppressive treatment (Al-Kharashi et al. 2007; Abu El-Asrar et al. 2008).

The principles of therapy for VKH disease are to suppress the initial intraocular inflammation in the acute posterior uveitis stage with early and aggressive use of systemic corticosteroids followed by slow tapering. Such treatment may shorten the duration of the disease, may prevent progression into the chronic stage and may also reduce the incidence of extraocular manifestations (Ohno et al. 1977; Rubsamen & Gass 1991; Moorthy et al. 1995). The intraocular inflammation will proceed to recurrent granulomatous anterior uveitis with typical 'sunset glow fundus' if not properly treated (Yang et al. 2007). Vision-threatening complications have clearly been recognized to occur in the chronic, recurrent phase of VKH disease, namely cataract, glaucoma, subretinal neovascular membranes and subretinal fibrosis. The occurrence of these complications is known to be associated with a worse visual outcome (Ohno et al. 1988; Moorthy et al. 1995; Read et al. 2001b; Al-Kharashi et al. 2007; Yang et al. 2007; Abu El-Asrar et al. 2008; Fang & Yang 2008).

Despite proper treatment with corticosteroids, several studies reported the development of chronic, recurrent granulomatous inflammation and 'sunset glow fundus' with peripapillary atrophy and depigmented small atrophic lesions at the level of retinal pigment epithelium (Al-Kharashi et al. 2007; Chee et al. 2007; Abu El-Asrar et al. 2008; Cuchacovich et al. 2010; Errera et al. 2011). The poor visual prognosis associated with chronic ocular inflammation and the well-documented ocular and systemic complications of long-term high-dose corticosteroid use have led many experts to suggest initiating immunomodulatory therapy early in the course of care of patients with VKH disease to achieve better control of the uveitis and to facilitate earlier tapering of corticosteroids (Fang & Yang 2008). Several studies suggested that the use of immunomodulatory therapy with cyclosporine, azathioprine, methotrexate and mycophenolate mofetil (MMF) early in the course of the disease is associated with good clinical results (Paredes et al. 2006; Kim & Yu 2007; Cuchacovich et al. 2010). Most of the studies involving immunomodulatory therapy have several limitations because of their retrospective nature. In addition, most studies evaluated the efficacy of several immunomodulatory agents collectively and included a mixture of patients in the acute uveitic phase and in the chronic recurrent phase.

Mycophenolate mofetil is an antimetabolite that has an increasing role in the treatment of autoimmune diseases and the prevention of solid organ transplant rejection. Its immunosuppressive activity is based on reversible inhibition of the inosine-5′-monophosphate dehydrogenase involved in the de novo pathway of purine synthesis. This ultimately prevents the replication of T and B lymphocytes (Srinivas et al. 2003; Appel et al. 2005). In this prospective study, we evaluated the effectiveness of MMF as first-line therapy combined with systemic corticosteroids in initial onset of acute uveitis associated with VKH disease. We compared the outcomes in this group with those of another group of patients with acute uveitis associated with VKH disease who were treated with corticosteroid monotherapy or with delayed addition of immunomodulatory therapy. The outcome of this group was previously reported (Al-Kharashi et al. 2007).

## Patients and Methods

In this prospective study, we evaluated patients diagnosed with VKH disease

**Table 1.** Relationship between initial visual acuity and final visual acuity for 38 eyes.

| | Initial visual acuity | | | | |
|---|---|---|---|---|---|
| Final visual acuity | CF | 20/200 | 20/50–20/100 | ≥20/40 | Total |
| ≥20/40 | 10 | 5 | 5 | 18 | 38 (100.0%) |
| 20/50–20/100 | 0 | 0 | 0 | 0 | 0 |
| 20/200 | 0 | 0 | 0 | 0 | 0 |
| CF | 0 | 0 | 0 | 0 | 0 |
| Total | 10 (26%) | 5 (13%) | 5 (13%) | 18 (48%) | 38 (100.0%) |

CF = counting fingers.

**Table 2.** Demographics, baseline characteristics and clinical outcomes in the corticosteroid and the corticosteroid + mycophenolate mofetil (MMF) groups.

| Variable | Corticosteroid group ($n$ = 68 patients) (%) | Corticosteroid + MMF group ($n$ = 19 patients) (%) | p-value |
|---|---|---|---|
| Age (years) | 25.04 ± 10.28 | 31.3 ± 8.5 | 0.0172* |
| Gender | | | |
| Female | 51 (75) | 10 (53) | 0.1097 |
| Male | 17 (25) | 9 (47) | |
| Interval between symptoms and treatment (days) | 49.8 ± 109 | 16.4 ± 13.1 | 0.0769 |
| Follow-up (months) | 34.4 ± 20.1 | 27.0 ± 11.1 | 0.1282 |
| | ($n$ = 136 eyes) (%) | ($n$ = 38 eyes) (%) | |
| Initial visual acuity of ≤20/200 | 48 (35) | 15 (40) | 0.7771 |
| Posterior synechiae at presentation | 34 (25) | 12 (32) | 0.545 |
| Anterior chamber reaction of >2+ at presentation | 56 (41) | 15 (40) | 0.998 |
| Final visual acuity of 20/20 | 51 (38) | 28 (74) | <0.001* |
| Recurrences of ≥3 times | 24 (18) | 1 (3) | 0.0383* |
| All complications | 58 (43) | 3 (8) | <0.001* |
| Cataract | 40 (29) | 1 (3) | 0.0013* |
| Glaucoma | 25 (18) | 2 (5) | 0.0852 |
| Subretinal neovascular membranes | 7 (5) | 0 (0) | 0.3494 |
| Subretinal fibrosis | 7 (5) | 0 (0) | 0.3494 |

* Statistically significant at 5% level of significance.

in the acute uveitic phase seen at King Abdulaziz University Hospital, Riyadh, Saudi Arabia. Diagnosis of VKH disease was based on the Revised International Diagnostic Criteria (Read et al. 2001a).

At presentation, all the patients had the following examination: best-corrected Snellen visual acuity, applanation tonometry, slit-lamp examination of the anterior segment, fundus biomicroscopy, indirect ophthalmoscopy, intravenous fluorescein angiography, indocyanine green angiography and optical coherence tomography.

All patients were managed and followed up by one of the authors (AMA). All patients received systemic corticosteroids combined with MMF 2 g daily. Corticosteroid therapy began with intravenous methylprednisolone 1 g/day for 3 days followed by oral prednisone (1 mg/kg of body weight/day) that was maintained for at least 3 weeks. The prednisone dose was gradually tapered following improvement of the intraocular inflammation to a maintenance dose of 5–10 mg/day. Prednisone was tapered at 10 mg every 2 weeks until a daily dose of 40 mg was reached. Afterwards, prednisone was tapered at 5 mg every 2 weeks, until 5–10 mg/day was reached. Anterior segment inflammation was treated with topical corticosteroids and cycloplegic agents. The clinical status, blood cell counts, liver and renal function tests were checked by internists every 6 weeks during the period of treatment. Corticosteroid-sparing effect, defined as reduction in the prednisone dose to 10 mg/day or less while maintaining inactive uveitis, and time to achievement of the effect were assessed (Jabs et al. 2005). Main outcome measures were final visual acuity, corticosteroid-sparing effect, development of multiple recurrences of three times or more, incidence of ocular complications and incidence of treatment-related side-effects.

### Statistical methods

Comparisons of means from two independent groups was made using Student's *t*-test. The Chi-square test or Fisher's exact test was used to compare two proportions from two independent groups. A p-value $< 0.05$ indicated statistical significance.

## Results

A total of 19 patients (38 eyes) with acute uveitis associated with VKH disease were enrolled in this study. Patients were 10 (53%) women, and nine (47%) were men, whose ages at presentation ranged from 12 to 44 years with a mean of 31.3 ± 8.5 years. Slit-lamp examination at presentation revealed mutton-fat keratic precipitates in 14 (37%) eyes. No obvious anterior chamber cells were observed in eight (20%) eyes. In the remaining 30 eyes, the anterior chamber reaction was graded as 1+ to 2+ in 15 (40%) eyes, and more than 2+ in 15 (40%) eyes (Jabs et al. 2005). Posterior synechiae of the iris were observed in 12 (32%) eyes. Fundus examination showed hyperaemia and swelling of the optic disc and exudative retinal detachment in all eyes. The interval between the onset of symptoms and starting treatment ranged from 2 to 42 days with a mean of 16.4 ± 13.1 days and a median of 7 days.

The follow-up period ranged from 16 to 54 months with a mean of

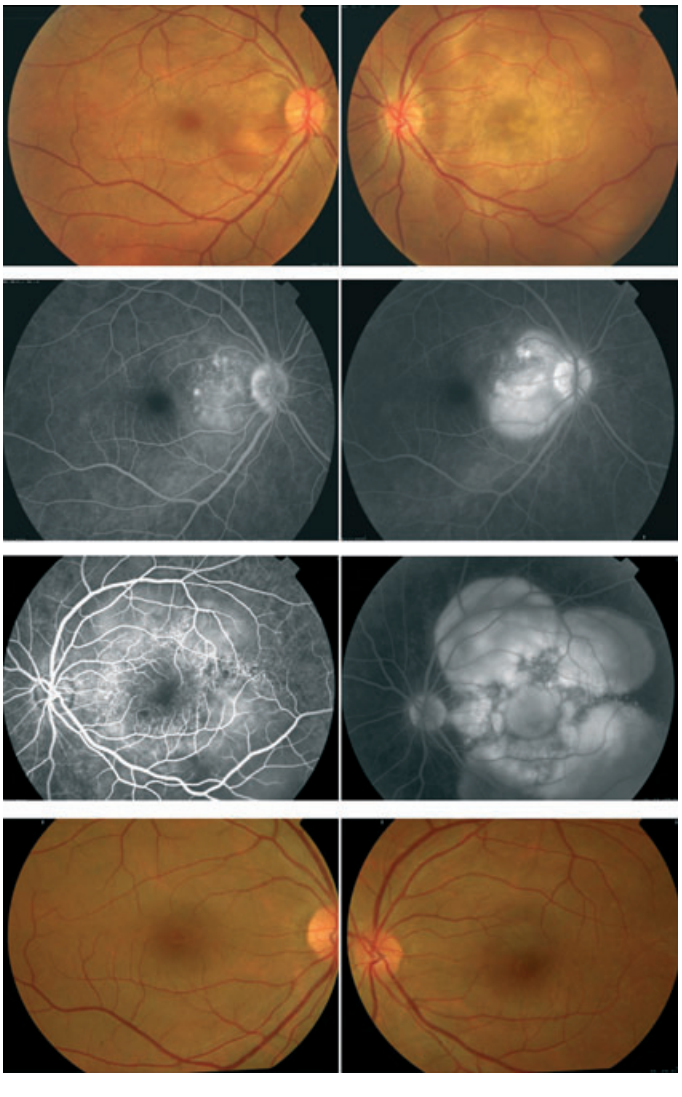

**Fig. 1.** A 27-year-old women with Vogt–Koyanagi–Harada disease in the acute uveitic phase. Note the exudative retinal detachments and the hyperaemic optic discs. Visual acuity was 20/20 in the right eye and counting fingers at two feet in the left eye (Top). Fluorescein angiography showed multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and late of pooling of dye in the areas of exudative retinal detachment (second and third rows). The patient received systemic corticosteroids combined with mycophenolate mofetil. Fifty-four months after treatment, best-corrected visual acuity was 20/20 in both eyes. Note the absence of 'sunset glow fundus' and chorioretinal atrophy (Bottom). The patient was off treatment for 41.5 months without relapse of inflammation.

27.0 ± 11.1 months and a median of 23 months. None of the patients missed their appointments during the follow-up period and none developed any systemic adverse events associated with the treatment. Corticosteroid-sparing effect was achieved in all patients. The interval between starting treatment and tapering prednisone to 10 mg or less per day ranged from 3 to 7 months with a mean of 5.1 ± 1.2 months and a median of 5 months. Ten (53%) patients were able to discontinue treatment without relapse of the inflammation. The duration of systemic corticosteroid therapy in these patients ranged from 8 to 15.5 months with a mean of 12.4 ± 2.8 months, and the duration of MMF therapy ranged from 12 to 21 months with a mean of 16.4 ± 3.7 months. These patients were off treatment for a period ranging from 3 to 41.5 months with a mean of 17.3 ± 11.9 months. At the last follow-up, nine patients were still taking prednisone 10 mg combined with MMF 500 mg daily. The follow-up in these patients ranged from 16 to 24 months with a mean of 20.2 ± 2.7 months.

The distribution of initial and final visual acuity is illustrated in Table 1. All the eyes achieved visual acuity of 20/40 or better. Table 2 shows the demographics, baseline characteristics and clinical outcomes of the corticosteroid and corticosteroid + MMF groups. In the corticosteroid group, 51 (38%) eyes achieved visual acuity of 20/20 compared with 28 (74%) eyes in the corticosteroid + MMF group. The difference between the two percentages was statistically significant ($p < 0.001$).

During the follow-up, one (3%) eye developed multiple recurrences manifested as anterior uveitis of three times or more in the corticosteroid + MMF group. In the corticosteroid group, 24 (18%) eyes developed multiple recurrences of three times or more. The difference between the two percentages was statistically significant ($p = 0.0383$). In the corticosteroid + MMF group, three (8%) eyes developed complications. The ocular complications encountered were glaucoma that necessitated medical therapy in two (5%) eyes, and cataract in one (3%) eye. Overall, 58 (43%) eyes developed at least one complication in the corticosteroid group. The difference between the two percentages was statistically significant ($p < 0.001$). None of the eyes in the corticosteroid + MMF group developed depigmentation of the fundus resulting in sunset glow fundus, peripapillary atrophy or areas of chorioretinal atrophy (Figs 1 and 2). All the eyes in the corticosteroid group developed 'sunset glow fundus' and multiple well-circumscribed areas of chorioretinal atrophy (Fig. 3). In addition, none of the patients in the corticosteroid + MMF group developed vitiligo, poliosis, alopecia or sensory hearing loss. In the corticosteroid group, 49% developed sensory hearing loss, 33% developed vitiligo, 21% developed alopecia and 10% developed poliosis.

## Discussion

Several studies reported that MMF is a safe and effective corticosteroid-sparing immunomodulatory agent in the treatment of noninfectious uveitis

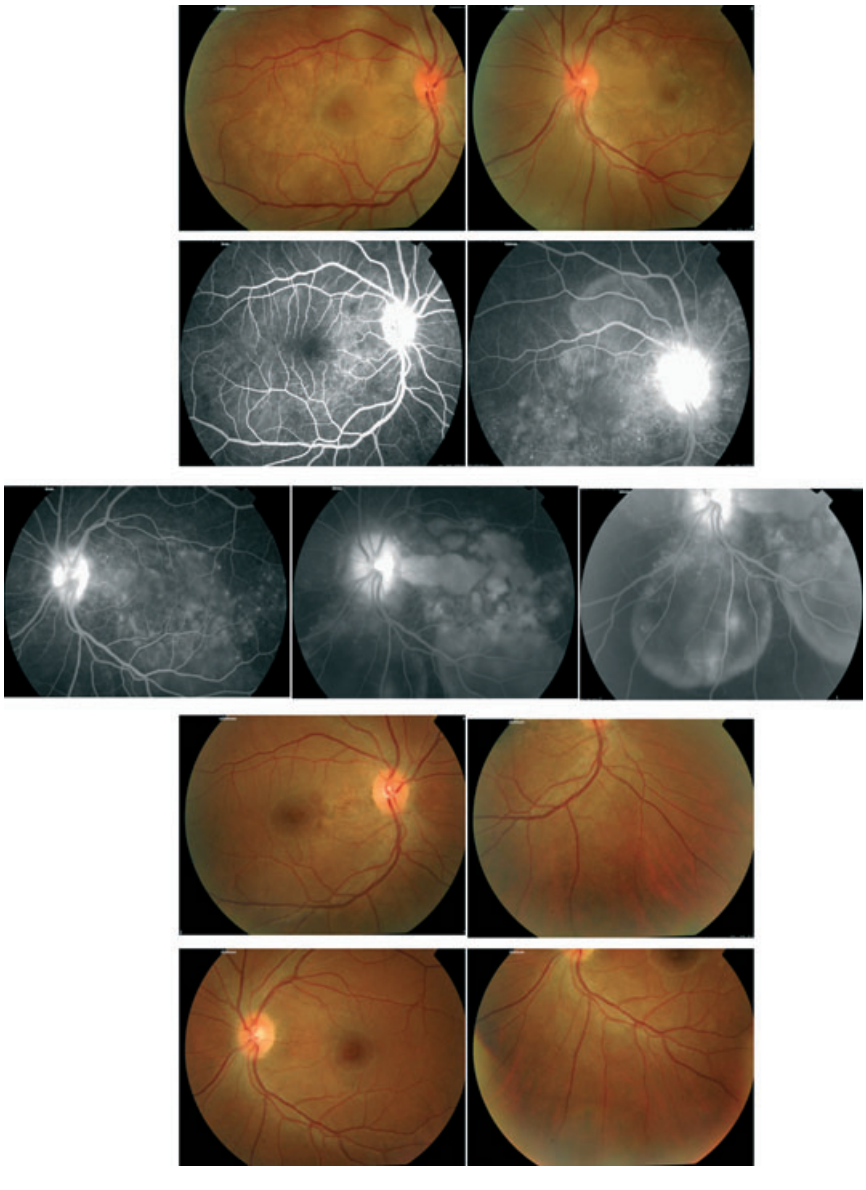

**Fig. 2.** A 28-year-old men with Vogt–Koyanagi–Harada disease in the acute uveitic phase. Note the exudative retinal detachments and the hyperaemic optic discs. Visual acuity was counting fingers at three feet in both eyes (Top). Fluorescein angiography showed multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and late of pooling of dye in the areas of exudative retinal detachment (second and third rows). The patient received systemic corticosteroids combined with mycophenolate mofetil. Thirty-two months after treatment, best-corrected visual acuity was 20/20 in both eyes. Note the absence of 'sunset glow fundus' and chorioretinal atrophy (fourth and fifth rows). The patient was off treatment for 18 months without relapse of inflammation.

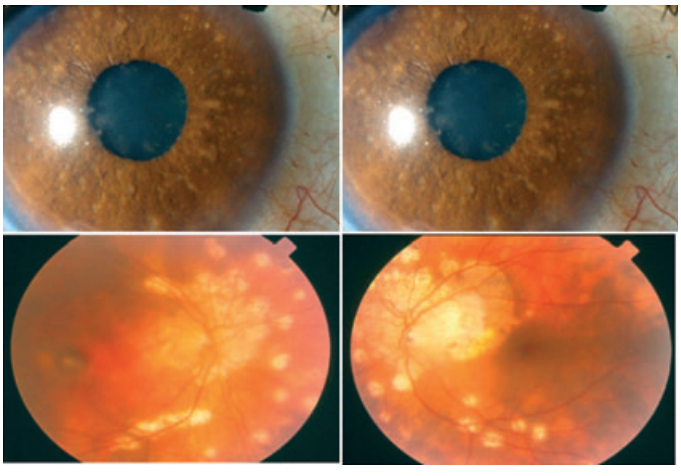

**Fig. 3.** A 22-year-old women with Vogt–Koyanagi–Harada disease in the corticosteroid group 10 years after onset of disease. Note the granulomatous anterior uveitis with development of iris nodules (Top), and 'sunset glow fundus', peripapillary chorioretinal atrophy and multiple areas of chorioretinal atrophy (Bottom).

(Baltazis et al. 2003; Lau et al. 2003; Siepmann et al. 2006; Teoh et al. 2008; Daniel et al. 2010). However, these studies were retrospective in nature and included mixtures of different clinical entities of endogenous uveitis. To the best of our knowledge, this is the first prospective study that investigated the role of MMF as first-line therapy combined with systemic corticosteroids in the treatment of initial onset of acute uveitis associated with VKH disease. One of the most important goals in using immunomodulatory therapy is to minimize exposure to corticosteroids and to reduce corticosteroid levels. In this series, a corticosteroid-sparing effect was achieved in all patients after a mean time of 5.1 ± 1.2 months. Corticosteroid withdrawal was achieved in 10 (53%) patients after a mean time of 12.4 ± 2.8 months without relapse of inflammation. Among those patients who discontinued treatment, the mean time observed off of treatment was 17.3 ± 11.9 months. In addition, we demonstrated that addition of MMF as first-line therapy to corticosteroids leads to significant reduction in recurrences of uveitis and development of complications and significantly improves visual outcome. Furthermore, MMF was effective in preventing the development of vitiligo, poliosis, alopecia and sensory hearing loss.

Several studies reported that many patients with VKH disease fare poorly with corticosteroid monotherapy. Despite proper treatment with corticosteroids, many patients develop chronic, recurrent granulomatous inflammation and 'sunset glow fundus' (Al-Kharashi et al. 2007; Lai et al. 2009; Cuchacovich et al. 2010; Errera et al. 2011). Patients with chronic recurrent granulomatous episodes of inflammation displayed more striking and long-lasting breakdown of the blood–aqueous barrier and more severe inflammation than initial onset of VKH patients. In addition, recurrent inflammation in the anterior segment is more refractory in patients with recurrent VKH disease (Fang et al. 2008). Several reports demonstrated a significant association between chronic anterior segment inflammation and poor final visual acuity and the development of long-term complications (Rubsamen & Gass 1991; Read et al. 2001b; Keino et al. 2002; Al-Kharashi et al. 2007). Thus, nonsteroid immunomodulatory therapy has become necessary in the treatment of the acute stage of VKH disease. Paredes et al. (2006) reported the outcome in 13 patients with VKH disease and suggested that the use of immunomodulatory therapy early in the course of the disease is associated with a superior visual outcome when compared to corticosteroids as monotherapy or with delayed addition of immunomodulatory therapy. However, long-term complications were not included in this study, and information is missing about clinical evolution after immunomodulatory therapy was withdrawn. In the present study, we demonstrated that the use of MMF as first-line therapy in acute uveitis associated with VKH disease reduced the development of chronic, recurrent inflammation and late complications and improved visual outcome.

There is accumulating evidence to suggest that despite proper treatment with corticosteroids, many patients develop progressive depigmentation of the fundus resulting in 'sunset glow fundus' appearance, even after the clinical disease appears to be under control (Keino et al. 2002, 2006; Al-Kharashi et al. 2007; Lai et al. 2009). Keino et al. (2002) demonstrated a significant association between the incidence of chronic ocular inflammation and the appearance of 'sunset glow fundus'. In addition, Bacsal et al. (2008) demonstrated concomitant subclinical choroidal inflammation associated with clinically isolated anterior segment recurrence. Furthermore, Kawaguchi et al. (2010) showed ongoing subclinical choroidal inflammation, despite apparent control of clinical signs. Their findings explain the development of 'sunset glow fundus' in seemingly controlled disease. In the present study, none of the patients developed 'sunset glow fundus' suggesting that MMF was effective in controlling progressive subclinical choroidal inflammation.

In conclusion, the use of MMF as first-line therapy combined with systemic corticosteroids is safe and effective in the treatment of acute uveitis associated with VKH disease. It has marked corticosteroid-sparing effect and significantly reduced the development of chronic recurrent inflammation and late complications. In addition, MMF significantly improved visual outcome. Our results suggest that MMF should be considered as first-line therapy for patients with acute uveitis associated with VKH disease.

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