Acta Ophthalmologica

Mycophenolate mofetil combined with systemic corticosteroids prevents progression to chronic recurrent inflammation and development of 'sunset glow fundus' in initial-onset acute uveitis associated with Vogt–Koyanagi–Harada disease

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ABSTRACT.

Purpose: **To evaluate the effectiveness and safety of mycophenolate mofetil (MMF) as first-line therapy combined with systemic corticosteroids in initial-onset acute uveitis associated with Vogt–Koyanagi–Harada (VKH) disease.**

Methods: **This prospective study included 38 patients (76 eyes). The main outcome measures were final visual acuity, corticosteroid-sparing effect, progression to chronic recurrent granulomatous uveitis and development of complications, particularly 'sunset glow fundus'.**

Results: **The mean follow-up period was 37.0 ± 29.3 (range 9–120 months). Visual acuity of 20/20 was achieved by 93.4% of the eyes. Corticosteroid-sparing effect was achieved in all patients. The mean interval between starting treatment and tapering to 10 mg or less daily was 3.8 ± 1.3 months (range 3–7 months). Twenty-two patients (57.9%) discontinued treatment without relapse of inflammation. The mean time observed off of treatment was 28.1 ± 19.6 months (range 1–60 months). None of the eyes progressed to chronic recurrent granulomatous uveitis. The ocular complications encountered were glaucoma in two eyes (2.6%) and cataract in five eyes (6.6%). None of the eyes developed 'sunset glow fundus', and none of the patients developed any systemic adverse events associated with the treatment.**

Conclusions: **Use of MMF as first-line therapy combined with systemic corticosteroids in patients with initial-onset acute VKH disease prevents progression to chronic recurrent granulomatous inflammation and development of 'sunset glow fundus'.**

Key words: immunomodulatory therapy – mycophenolate mofetil – recurrence – 'sunset glow fundus' – Vogt–Koyanagi–Harada disease

Acta Ophthalmol. 2017: 95: 85–90

doi: 10.1111/aos.13189

Introduction

Uveitis associated with Vogt–Koyanagi–Harada (VKH) disease is an autoimmune disease directed against one or more antigens found on or associated with uveal melanocytes (Yamaki et al. 2000a,b; Gocho et al. 2001). The initial-onset acute disease typically exhibits granulomatous choroiditis with exudative retinal detachment and optic disc hyperaemia and swelling, subsequently involving the anterior segment and finally developing into chronic recurrent granulomatous anterior uveitis if not properly treated with typical 'sunset glow fundus' and chorioretinal atrophy (Yang et al. 2007; Fang & Yang 2008; Abu El-Asrar et al. 2013). Vogt–Koyanagi–Harada (VKH) disease commonly affects pigmented races and people of certain genetic predisposition (Moorthy et al. 1995; Fang & Yang 2008) and is one of the most common uveitis entities in Saudi Arabia (Al Dhahri et al. 2014).

Vision-threatening complications have clearly been recognized to occur in the chronic recurrent phase of VKH disease, namely cataract, glaucoma, subretinal neovascular membranes, subretinal fibrosis, chorioretinal atrophy and 'sunset glow fundus'. 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. 2001a; Al-Kharashi et al. 2007; Yang et al. 2007; Abu El-Asrar et al. 2008, 2013; Fang & Yang 2008). Several studies showed a significant association between the incidence of chronic recurrent ocular inflammation and the development of 'sunset glow fundus'

(Keino et al. 2002; Abu El-Asrar et al. 2013; Lee et al. 2015).

The main goals in management of initial-onset acute VKH disease are to suppress the intraocular inflammation in the acute posterior uveitis stage and prevention of the progression to chronic recurrent intraocular inflammation. Despite appropriate treatment with early high-dose systemic corticosteroids, many patients develop chronic recurrent granulomatous inflammation and 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; Al-Kharashi et al. 2007; Chee et al. 2007; Abu El-Asrar et al. 2008; Errera et al. 2011; Sakata et al. 2015). The progression of 'sunset glow fundus' despite the use of proper corticosteroid monotherapy suggests the presence of inadequately controlled choroidal inflammation.

The poor visual prognosis associated with chronic recurrent inflammation and the well-documented ocular and systemic complications of long-term high-dose corticosteroid treatment have led many uveitis specialists to recommend initiating non-steroidal immunomodulatory therapy with cyclosporine, azathioprine, methotrexate and mycophenolate mofetil (MMF) early in the course of the disease to achieve better control of the uveitis and to facilitate earlier tapering of corticosteroids (Paredes et al. 2006; Kim & Yu 2007; Fang & Yang 2008; Cuchacovich et al. 2010; Abu El-Asrar et al. 2012, 2013). In a previous prospective study of 19 patients with acute VKH disease, we demonstrated that addition of MMF as first-line therapy to corticosteroids significantly improved the clinical outcomes (Abu El-Asrar et al. 2012).

In this prospective study of 38 patients with initial-onset acute uveitis associated with VKH disease, we extended our previous report to evaluate the long-term effectiveness of MMF as first-line therapy combined with systemic corticosteroids in preventing the progression to chronic recurrent intraocular inflammation and the development of 'sunset glow fundus'.

Patients and Methods

In this prospective study, we evaluated patients diagnosed with initial-onset acute uveitis associated with VKH disease seen in the Uveitis Clinic of King Abdulaziz University Hospital, Riyadh, Saudi Arabia. Diagnosis of VKH disease was based on the Revised International Diagnostic Criteria (Read et al. 2001b).

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 (OCT).

All patients were managed and followed up by one of the authors (AMA). All patients received systemic corticosteroids combined with MMF 2 g daily (600 mg/m^2 twice daily for children) as first-line therapy. Corticosteroid therapy began with intravenous methylprednisolone 1 g/day (15–30 mg/kg of body weight for children) 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. In general, 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. Similarly, the MMF dose was gradually tapered after the patients had complete remission to a maintenance dose of 500 mg/day. 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 of 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, progression to chronic recurrent granulomatous uveitis, and development of complications, particularly, 'sunset glow fundus'.

Statistical methods

Data were collected and stored in a spreadsheet using MICROSOFT EXCEL 2010® software. Data management and coding were then done in Excel. Data were analysed using SPSS® version 20.0 (IBM Inc., Chicago, IL, USA). Descriptive analysis was primarily carried out, where categorical variables were presented in the form of frequencies and percentages and continuous variables in the form of mean (±standard deviation). Data were analysed using *t*-test and Mann–Whitney *U*-test. A p-value <0.05 indicated statistical significance.

Results

A total of 38 patients (76 eyes) with initial-onset acute uveitis associated with VKH disease were included. Patients were 21 males (55%), and 17 females (45%). The age at presentation ranged from 7 to 44 years with a mean of 27.7 ± 10.3 years. There were six patients (16%) who were 16 years of age or younger. All eyes typically showed exudative retinal detachment and optic disc hyperaemia and swelling (Figs 1 and 2). The interval between the onset of symptoms and presentation ranged from 1 to 30 days with a mean of 9.9 ± 8.6 days and a median of 7 days.

The follow-up period ranged from 9 to 120 months with a mean of 37.0 ± 29.3 months and a median of 27 months. None of the patients missed his appointments during the follow-up period. The distribution of initial and final visual acuity is illustrated in Table 1. The prevalence of best vision of 20/20 significantly increased from 26.3% of the eyes at presentation to 93.4% of the eyes at last follow-up ($p < 0.001$; *t*-test). The prevalence of worst vision of 20/200 or less significantly reduced from 32.8% of the eyes at presentation to 0.0% of the eyes at last follow-up ($p < 0.001$; *t*-test).

None of the eyes progressed to chronic recurrent granulomatous anterior uveitis. The ocular complications encountered were glaucoma that necessitated medical therapy in two eyes (2.6%) and cataract in five eyes (6.6%). None of the eyes developed depigmentation of the fundus resulting in 'sunset glow fundus', peripapillary atrophy or areas of chorioretinal atrophy (Figs 1 and 2). Two patients (2.6%) developed vitiligo and poliosis.

Corticosteroid-sparing effect was achieved in all patients. The interval

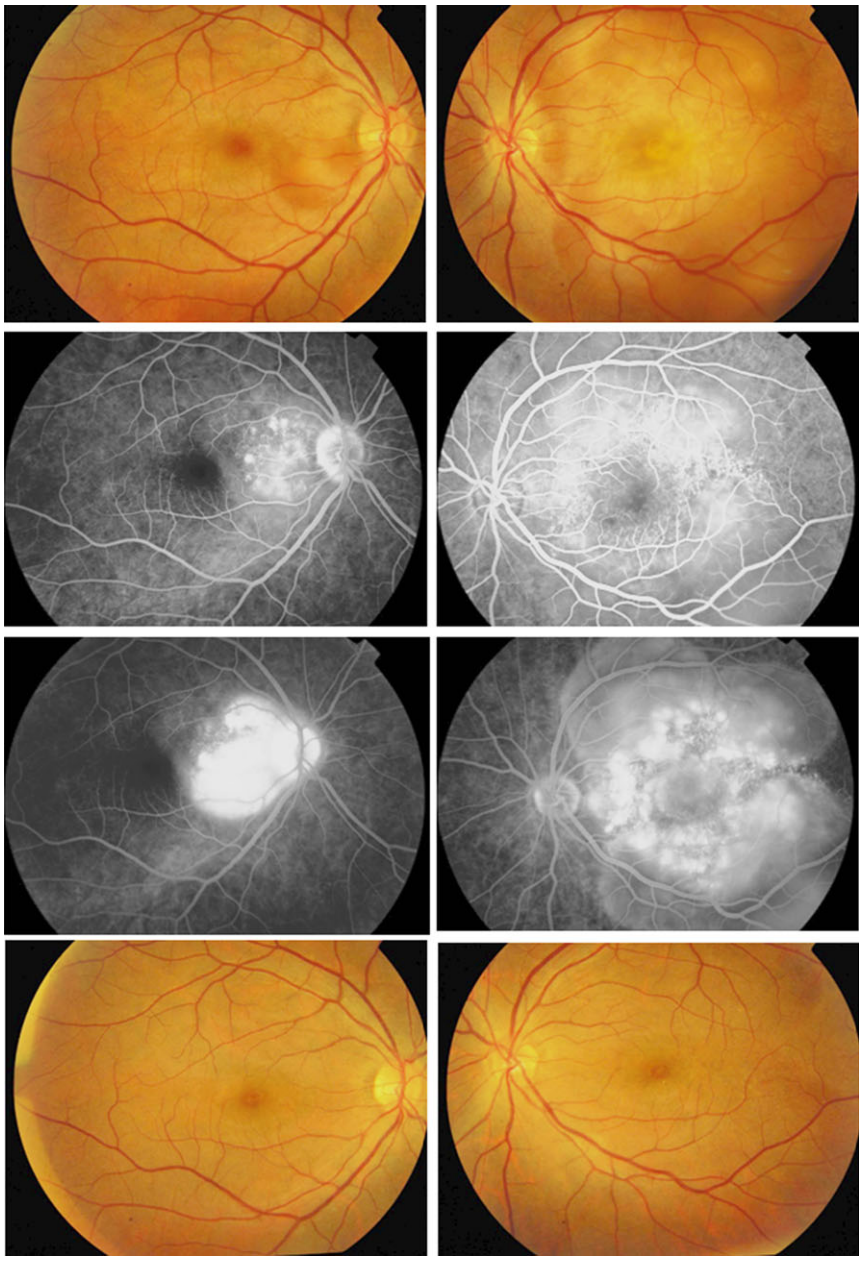

Fig. 1. A 38-year- old man with initial-onset acute Vogt–Koyanagi–Harada (VKH) disease at presentation. Note the exudative retinal detachments and the hyperaemic optic discs. Visual acuity was 20/20 in the right eye and counting figures, at 2 feet in the left eye (top). Fluorescein angiography shows multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and late pooling of dye in the areas of exudative retinal detachment (second and third rows). The patient received systemic corticosteroids combined with mycophenolate mofetil. Thirty-six 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 12 months without relapse of inflammation.

between starting treatment and tapering prednisone to 10 mg or less per day ranged from 3 to 7 months with a mean of 3.8 ± 1.3 months and a median of 4.0 months. Twenty-two patients (57.9%) were able to discontinue treatment without relapse of inflammation. The duration of systemic corticosteroid therapy in these patients ranged from 10 to 34 months with a mean of 18.7 ± 8.8 months and a median of 17.5 months. The duration of MMF therapy ranged from 9 to 34 months with a mean of 20.1 ± 7.7 months and a median of 20.2 months. These patients were off treatment for a period ranging from 1 to 60 months with a mean of 28.1 ± 19.6 months and a median of 25.5 months. In these 22 patients, there was a trend for a longer duration of systemic corticosteroid therapy (range 14–34; mean 22.8 ± 8.5; median 21.5 months) in patients with a longer interval between the onset of symptoms and presentation (more than 7 days) compared to patients with a shorter interval of 7 days or less (range 10–26; mean 16.3 ± 6.2; median 15.0 months). However, the difference was not statistically significant ($p = 0.147$; Mann–Whitney *U*-test). Similarly, the duration of MMP therapy was longer (range 14–34; mean 23.5 ± 8.2; median 23.0 months) in patients with a longer interval between onset of symptoms and presentation compared to patients with a shorter interval (range 9–29; mean 17.1 ± 7.9; median 14.0 months). However, the difference was not statistically significant ($p = 0.218$; Mann–Whitney U-test). At the last follow-up, 10 patients were still taking prednisone 10 mg or less combined with MMF 500 mg daily and six patients were still taking prednisone 10 mg or less combined with MMF 2 g daily.

Discussion

Vogt–Koyanagi–Harada (VKH) disease typically begins with granulomatous choroiditis associated with exudative retinal detachment and optic disc hyperaemia and swelling. The disease will proceed to chronic recurrent granulomatous anterior uveitis if not properly treated with typical 'sunset glow fundus' appearance and chorioretinal atrophy (Yang et al. 2007; Fang & Yang 2008; Abu El-Asrar et al. 2013). There is accumulating evidence to suggest that despite proper treatment with corticosteroid monotherapy, many patients develop chronic recurrent granulomatous inflammation and progressive depigmentation of the fundus resulting in 'sunset glow fundus' appearance and chorioretinal atrophy, even after the clinical disease appears to be under control (Keino et al. 2002; Al-Kharashi et al. 2007; Chee et al. 2007; Abu El-Asrar et al. 2008; Errera et al. 2011; Sakata et al. 2015). Recently, Sakata et al. (2015) demonstrated that in spite of early high-dose corticosteroid therapy within 30 days from disease onset and a slow taper, 79% of patients with

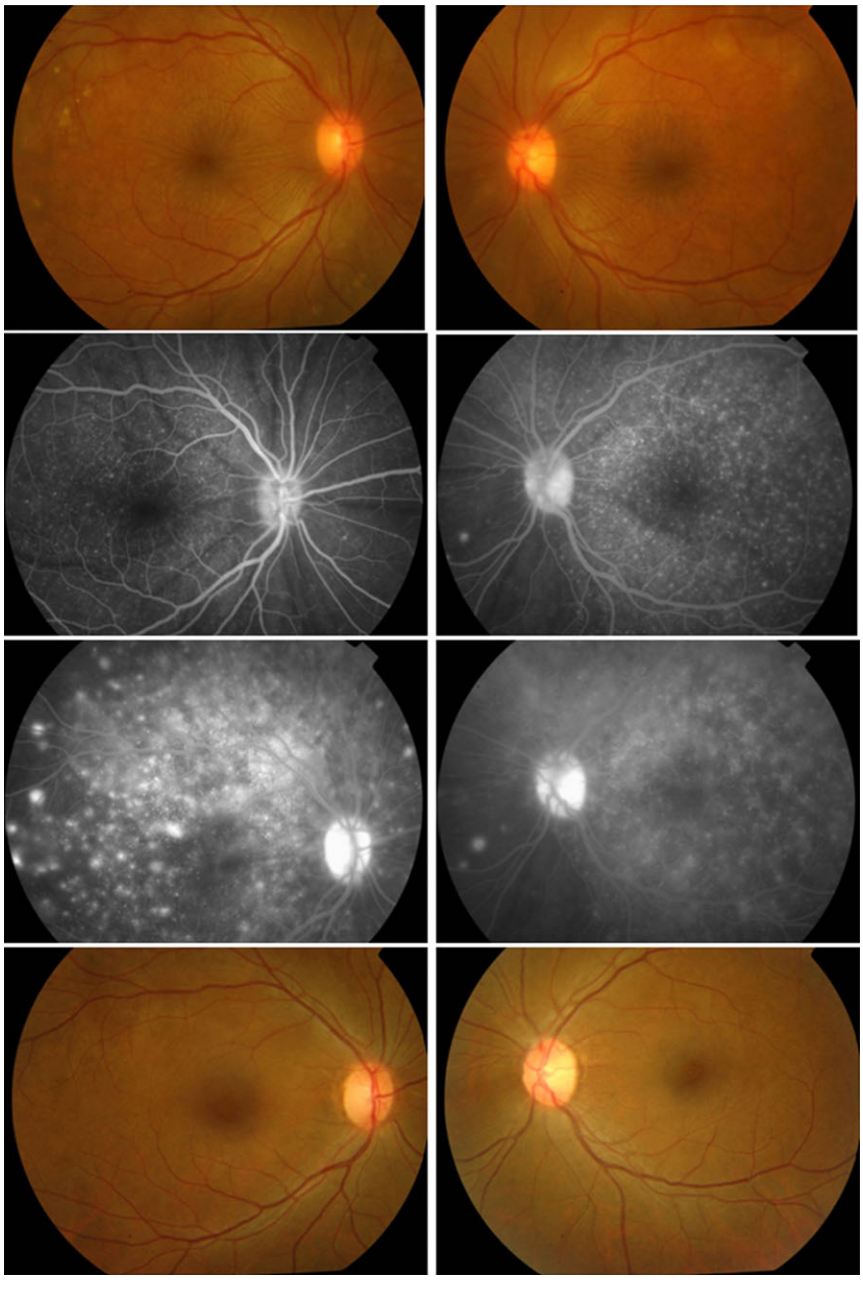

Fig. 2. A 37-year-old woman with initial-onset acute Vogt–Koyanagi–Harada (VKH) disease at presentation. Note the exudative retinal detachments and the hyperaemic optic discs. Visual acuity was 20/100 in the right eye and 20/40 in the left eye (top). Fluorescein angiography shows multiple hypofluorescent choroidal folds radiating from the optic discs and multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and late 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 16 months without relapse of inflammation.

VKH disease progressed to chronic recurrent disease, and 38% developed subretinal fibrosis. Similarly, Chee et al. (2007) observed that one-third of patients receiving high-dose corticosteroid therapy within 2 weeks of onset progressed to chronic recurrent disease. Keino et al. (2002) demonstrated that despite high-dose corticosteroid therapy at the initial onset, 17.5% of patients developed chronic ocular inflammation. Chronic recurrent VKH disease is significantly associated with more severe anterior segment inflammation at presentation and a worse visual acuity and mean retinal sensitivity at last follow-up compared with initial-onset acute VKH disease (Abu El-Asrar et al. 2013, 2016). Studies using laser flare-cell meter demonstrated that both aqueous flare values and cell counts were significantly higher in patients with chronic recurrent VKH disease than those with initial-onset acute VKH disease. Furthermore, chronic recurrent granulomatous inflammation in the anterior segment is more refractory to treatment (Fang et al. 2008). Consequently, complications are more common in patients with chronic recurrent VKH disease who present with recurrent granulomatous anterior uveitis with 'sunset glow fundus' (Yang et al. 2007; Abu El-Asrar et al. 2013). In the present study, we demonstrated that addition of immunomodulatory therapy with mycophenolate mofetil as first-line therapy combined with systemic corticosteroids in patients with initial-onset acute VKH disease prevents progression of the disease to chronic recurrent granulomatous anterior uveitis and development of 'sunset glow fundus'.

Keino et al. (2006) followed 102 patients with VKH disease from initial-onset who were treated with high-dose corticosteroid therapy. 'Sunset glow fundus' developed in 67.6% of the patients. The mean duration until the appearance of 'sunset glow fundus' was 4.2 ± 2.7 months. Similarly, Lai et al. (2009) demonstrated the development of 'sunset glow fundus' in 51.4% of patients who received oral corticosteroids during the first attack of VKH disease. Several studies reported the significant association between the incidence of chronic ocular inflammation and the development of 'sunset glow fundus' (Keino et al. 2002; Abu El-Asrar et al. 2013; Lee et al. 2015). Indocyanine green angiographic studies of patients during episodes of apparent isolated granulomatous anterior segment recurrence showed concomitant subclinical choroidal inflammation despite the absence of clinical signs of posterior segment involvement (Bacsal et al. 2008; Takemoto et al. 2016). In addition, histopathologic analysis of eyes with 'sunset glow fundus' in patients with VKH disease revealed the presence of scattered inflammatory infiltrate of predominantly T lymphocytes in the thickened choroid with notable disappearance of choroidal melanocytes (Inomata & Sakamoto 1990). These

Table 1. Relationship between initial visual acuity and final visual acuity for 76 eyes.

Final visual acuity	Initial visual acuity					Total
	CF	20/200	20/50–20/100	20/30–20/40	20/20	
20/20	12	12	16	12	19	71 (93.4%)
20/30–20/40	1	0	1	1	1	4 (5.3%)
20/50–20/100	0	0	1	0	0	1 (1.3%)
20/200	0	0	0	0	0	0
CF	0	0	0	0	0	0
Total	13 (17.1%)	12 (15.8%)	18 (23.7%)	13 (17.1%)	20 (26.3%)	76 (100%)

CF = counting fingers.

findings suggest that ongoing subclinical choroidal inflammation due to inadequate immunosuppression is involved in the pathogenesis of progressive posterior segment depigmentation resulting in 'sunset glow fundus' appearance and chorioretinal atrophy (Bacsal et al. 2008; Kawaguchi et al. 2010). In previous studies, we identified a significant association between the development of 'sunset glow fundus' and a worse final visual acuity (Abu El-Asrar et al. 2013) and mean retinal sensitivity (Abu El-Asrar et al. 2016). In addition, the development of 'sunset glow fundus' was significantly associated with the development of any complication of cataract or glaucoma or subretinal neovascular membranes (Abu El-Asrar et al. 2013). Therefore, prevention of the development of 'sunset glow fundus' may result in better visual function in patients with VKH disease. In the present study, none of the patients developed 'sunset glow fundus' suggesting that the use of immunomodulatory therapy with MMF as first-line therapy combined with systemic corticosteroids in patients with initial-onset acute VKH disease was effective in controlling progressive subclinical choroidal inflammation.

One of the most important goals in using non-steroidal immunomodulatory therapy in non-infectious uveitis is to minimize exposure to corticosteroids and to reduce corticosteroid levels. Several studies reported that MMF is safe and effective corticosteroid-sparing immunomodulatory agent in the treatment of non-infectious uveitis (Siepmann et al. 2006; Teoh et al. 2008; Daniel et al. 2010; Chang et al. 2011; Doycheva et al. 2011). However, these studies were retrospective in nature and included mixtures of different clinical entities of endogenous uveitis. In this prospective study, MMF was used as first-line therapy combined with systemic corticosteroids in the treatment of initial-onset acute uveitis associated with VKH disease. In this series, a corticosteroid-sparing effect (prednisone dose ≤10 mg daily) was achieved in all patients after a mean time of 3.8 ± 1.3 months. Corticosteroid withdrawal was achieved in 22 patients (57.9%) after a mean time of 18.7 ± 8.8 months without relapse of inflammation. Among those patients who discontinued treatment, the mean time observed off of treatment was 28.1 ± 19.6 months.

In conclusion, the use of MMF as first-line therapy combined with systemic corticosteroids in patients with initial-onset acute VKH disease prevents progression of the disease to chronic recurrent granulomatous anterior uveitis and development of 'sunset glow fundus' and chorioretinal atrophy. These findings suggest that MMF is effective in controlling progressive subclinical choroidal inflammation. In addition, MMF is safe and has marked corticosteroid-sparing effect.

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Received on February 7th, 2016.
Accepted on June 13th, 2016.

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The authors thank Professor Carl Herbort, Inflammatory and Retinal Eye Diseases, Centre for Ophthalmic Specialized Care and Department of Ophthalmology, University of Lausanne, Lausanne, Switzerland, for helpful suggestions and discussions. The authors also thank Ms. Connie B. Unisa-Marfil and Mrs. Fe Suarez for secretarial work. This work was supported by King Saud University through Vice Deanship of Research Chair (Dr. Nasser Al-Rashid Research Chair in Ophthalmology).