TREATMENT OPTIONS IN VKH

VKH is an autoimmune, multi-system, granulomatous inflammatory disease involving the eye, auditory, cutaneous and neurological system. The exact mechanism of VKH is unknown. However, it has been postulated to affect an autoimmune response mediated by T-lymphocytes against an antigen found on, or associated with melanocytes. In the past, VKH was classified into: Vogt-Koyanagi disease and Harada disease. Vogt-Koyanagi was characterised by anterior uveitis, alopecia, poliosis, dysacusis and paralimbal vitiligo. Harada disease manifested with posterior segment changes and pleocytosis of cerebral spinal fluid. With Revised International Diagnostic Criteria (Table 1), VKH is now seen as a single disease entity.

TABLE 1. Diagnostic Criteria for Vogt-Koyanagi-Harada Disease

Complete Vogt-Koyanagi-Harada disease (criteria 1 to 5 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis.
2. No clinical or laboratory evidence suggestive of other ocular disease entities.
3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined).
a. Early manifestations of disease.
(1) There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disk hyperemia), which may manifest as one of the following:
(a) Focal areas of subretinal fluid, or
(b) Bullous serous retinal detachments.
(2) With equivocal fundus findings; both of the following must be present as well:
(a) Focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within subretinal fluid, and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography, and
(b) Diffuse choroidal thickening, without evidence of posterior scleritis by ultrasonography.
b. Late manifestations of disease.
(1) History suggestive of prior presence of findings from 3a, and either both (2) and (3) below, or multiple signs from (3):
(2) Ocular depigmentation (either of the following manifestations is sufficient):
(a) Sunset glow fundus, or
(b) Sugiura sign.
(3) Other ocular signs:
(a) Nummular chorioretinal depigmented scars, or
(b) Retinal pigment epithelium clumping and/or migration, or
(c) Recurrent or chronic anterior uveitis.
4. Neurological/auditory findings (may have resolved by time of examination).
a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors; headache alone is not sufficient to meet definition of meningismus, however), or
b. Tinnitus, or
c. Cerebrospinal fluid pleocytosis.
5. Integumentary finding (*not* preceding onset of central nervous system or ocular disease).
a. Alopecia, or
b. Poliosis, or
c. Vitiligo.
Incomplete Vogt-Koyanagi-Harada disease (criteria 1 to 3 and either 4 or 5 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis, and
2. No clinical or laboratory evidence suggestive of other ocular disease entities, and
3. Bilateral ocular involvement.
4. Neurologic/auditory findings; as defined for complete Vogt-Koyanagi-Harada disease above, or
5. Integumentary findings; as defined for complete Vogt-Koyanagi-Harada disease above.
Probable Vogt-Koyanagi-Harada disease (isolated ocular disease; criteria 1 to 3 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis.
2. No clinical or laboratory evidence suggestive of other ocular disease entities.
3. Bilateral ocular involvement as defined for complete Vogt-Koyanagi-Harada disease above.

Adapted from Read RW, Holland GN, Rao NA, Tabbara KF, Ohno S, Arellanes-Garcia L, Pivetti-Pezzi P, Tessler HH, Usui M. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. American journal of ophthalmology. 2001 May 31;131(5):647-52.

The treatment goal in VKH is to suppress the inflammatory response of the disease. Steroid therapy is the first line of immunosuppressive therapy for VKH. Posterior segment involvement requires Intravenous Methylprednisolone followed by oral steroids. Patients with an ocular manifestation of VKH need maintenance therapy of steroids for at least six months. Lai TY et al reported that patients receiving treatment for less than six months were more likely to have recurrences (58.8%) compared to those treated for six months or more (11.1%). Long duration and slow tapering of systemic steroids shorten the duration of the disease, reduce the incidence of extraocular manifestation of VKH and prevent the chronic stage associated with poor visual outcome. Vision-threatening complications such as cataract, subretinal neovascularisation, subretinal fibrosis and glaucoma have been recognized to occur in recurrent and chronic phases. Recurrence could lead to a chronic phase, "sunset glow" appearance and atrophic lesions at the retinal pigment epithelium (RPE).

Although effective as an immunosuppressant, steroids are associated with various ocular and systemic complications. At times, it proves to be difficult to determine the dose and duration of steroids which would be optimally effective in treating VKH with minimal side effects. For an example, in patients with poor glycaemic control while on steroids, fast tapering is essential to prevent debilitating consequences of hyperglycaemia. However, rapid tapering of steroids would compromise treatment of VKH. Hence, non-steroidal immunomodulatory therapy (IMT) is often required to replace steroids in treating

VKH. Moreover, IMT can also be useful in patients with a recurrence of VKH despite adequate corticosteroids treatment. Patients who do not respond to steroids or are steroid-resistant would also benefit with IMT to prevent chronic intraocular inflammation and its complications that are associated with reduced visual outcome.

The American Uveitis Society concludes that VKH requires IMT to control the inflammation. International Uveitis Study Group (IUSG) consensus panel has categorized VKH in the list of diseases for which immunosuppressive chemotherapy is considered "mandatory". Several studies have shown favourable results in treating VKH with cyclosporine, cyclophosphamide, chlorambucil, azathioprine, methotrexate and mycophenolate mofetil (MMF). Parades et al did a retrospective study that concluded, an early initiation of IMT (within six months of onset) was associated with better visual outcomes compared to those on steroid monotherapy or delayed initiation of IMT. Agarwal et al reported the use of triple immunosuppressive therapy (a combination of oral prednisolone, azathioprine and cyclosporine) in 5 patients who were refractory to previous steroid monotherapy. These patients immediately responded well to the triple therapy with rapid resolution. This retrospective study further proves that IMT, as an adjunct treatment to steroids, is effective in treating VKH.

Cyclosporine A has shown to be effective in treating sight-threatening non-infectious ocular inflammation. However, it can cause nephrotoxicity even at low doses. Therefore, this might not be the best drug for uncontrolled diabetic, hypertensive and elderly patients. Azathioprine and Cyclophosphamide A are effective alternatives for steroid-sparing agents in treating VKH. Methotrexate is the drug of choice for paediatric VKH cases. Soheilian et al reported that oral methotrexate is safe and effective as a steroid-sparing agent in controlling inflammation in paediatric VKH-associated panuveitis. Chlorambucil has shown to be a reasonable option in recalcitrant vision-threatening uveitis. Several IMT drugs are teratogenic such as methotrexate, chlorambucil and cyclophosphamide A. For women in the reproductive age group, these drugs would not be suitable as second-line treatment. MMF is shown to be tolerated by most patients with inflammatory eye disease with the most frequent side effect being gastrointestinal upset. Several studies have shown MMF to be safe and effective as a corticosteroid-sparing agent in non-infectious uveitis. The first prospective study by El-Asrar et al used MMF as a first-line therapy combined with systemic corticosteroids in the initial onset of acute uveitis in VKH patients. The study showed the corticosteroid-sparing effect was achieved in all patients within five to six months. Fewer patients had chronic, recurrent inflammation or late complications of VKH. They also had improved visual outcomes. Furthermore, MMF was effective in preventing the development of vitiligo, poliosis, alopecia and sensory-neural hearing loss. The results of the study proved that MMF can be used as a second line therapy in acute uveitis in VKH disease.

Corticosteroids remain the mainstay treatment of VKH however second-line therapy in VKH must be considered in patients who developed complications of steroids. The choice of IMT drug must be tailored for each patient according to the safety profile, patients' tolerability, age, gender, underlying medical illness and the course of the VKH disease itself. The options for treatment of VKH is growing. Besides IMT, other options for treatment of VKH are anti-tumour necrosis factor alpha (anti- TNF), anti-VEGF (vascular endothelial growth factor) agents and I.V. immunoglobulins. These can be used in intractable cases of inflammatory ocular disease which do not respond to steroids or IMT. With an appropriate choice of therapy, VKH can be successfully managed with a high chance of preventing extraocular manifestations, recurrence of inflammation and a chronic phase. This would ensure a high possibility of good visual outcome for the patients.

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