Vogt–Koyanagi–Harada is a Curable Autoimmune Disease: Early Diagnosis and Immediate Dual Steroidal and Non-Steroidal Immunosuppression are Crucial Prerequisites

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Abstract

Purpose: It is crucial to subdivide Vogt–Koyanagi–Harada (VKH) disease into two subentities, initial-onset disease versus chronically evolving disease. For early diagnosis and precise follow-up of VKH chorioiditis, the “Revised criteria for VKH” are no more sufficient for the appraisal of VKH and new biomarkers for disease activity are needed. It has been shown that, if initial-onset disease is treated promptly within the “therapeutic window of opportunity” and long enough with dual steroidal and non-steroidal immunosuppression, the disease can be cured in a large proportion of cases, an approach still contested. The proportion of chronic evolution and/or sunset-glow fundus (SGF) following steroidal monotherapy versus dual steroidal and non-steroidal immunosuppression was compared.

Methods: A literature search was performed, identifying studies on initial-onset VKH treated either by steroidal monotherapy or dual immunosuppression. Evolution toward chronicity and/or SGF was compared in both groups.

Results: Twenty studies were identified with reported long-term outcomes. In 16 studies, 802 patients received steroidal monotherapy, while in 4 studies, 172 patients received dual steroidal and non-steroidal immunosuppression. Chronic evolution and SGF occurred, respectively, in 44% and 59% in the corticosteroid-alone group versus 2.3% and 17.5% in the dual therapy group with no chronic evolution in three studies and no SGF in two studies.

Conclusions: Chronic evolution and SGF are significantly less frequent in initial-onset VKH when treated with immediate dual steroidal and non-steroidal immunosuppression with a high proportion of healed cases. This combined approach seems recommended in the management of initial-onset VKH disease.

Keywords: Chronic evolution, Dual immunosuppression, Sunset-glow fundus, Vogt–Koyanagi–Harada disease

INTRODUCTION

Vogt–Koyanagi–Harada (VKH) disease is an autoimmune-driven inflammation of ocular, auditory, and meningeal structures that all contain melanocytes, the elective target of the inflammatory reaction.1,2 The first structure to be involved in this process is the melanocyte islets in the choroidal stroma, where a stromal choroiditis develops.3,4 This inflammatory reaction can be detected early by investigational methods that reveal subclinical signs of choroidal inflammation such as spectral-domain optical coherence tomography (OCT) or indocyanine green angiography (ICGA).5,6

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Such an early stage of the disease is accompanied by prodromal symptoms that can include headaches, auditory symptoms, and meningeal signs and symptoms.\(^3\)\(^8\)

In case the early stage of disease is missed and/or not treated, the inflammatory process is spilling over and involves secondarily other ocular structures such as the optic disc and the retina, in a further step progressing to a granulomatous panuveitis and to chronic disease.\(^9\)

It is crucial to distinguish between the early initial-onset stage of disease and the later chronically evolving disease because the impact of therapeutic intervention appears to be different whether applied to acute initial-onset disease or chronically evolving disease. In many past studies and attempts to classify VKH, this important distinction was overlooked.\(^10\)

It was shown that the disease can be cured when treatment is initiated at an early stage, within the therapeutic window of opportunity,\(^11\) whereas treatment has to be prolonged and is less successful when intervening on already chronically evolving disease.\(^12\) Early treatment is not the only prerequisite to attempt a cure of the disease. There is growing evidence that the conventional treatment by systemic corticosteroid, even when given early and at adequate dosage, is not sufficient to prevent chronic evolution.\(^13\) An increasing number of reports have become available that show that dual steroidal and non-steroidal immunosuppression given at the stage of initial-onset VKH is needed to prevent chronic evolution and represent an opportunity to cure the disease.\(^14\) The aim of this study was to analyze and compare on one side studies on the treatment of initial-onset disease managed with steroid-only therapy to studies that used combined (dual) steroidal and non-steroidal immunosuppression.

**METHODS**

A literature search on the PubMed database was performed, using the search term Vogt-Koyanagi-Harada. Every article or part of an article giving clear information on whether the cases reported were initial-onset disease was considered. It included observational studies, clinical trials, and case series, but no reviews. Additional inclusion criteria comprised (1) clear indication of the treatment performed at the moment of presentation, either corticosteroid monotherapy or corticosteroids associated with immunosuppressive therapy, and (2) whether there was clear information on the rate of chronic evolution and/or sunset-glow fundus. Studies were subdivided into two groups according to whether they had been treated with systemic corticosteroids alone or dual steroidal and non-steroidal treatment.

**RESULTS**

Up to June 30, 2019, 1249 articles referenced in the PubMed database contained the term Vogt-Koyanagi-Harada. Twenty studies or part of series were eligible as they responded to the required criteria: (1) they concerned only acute initial-onset patients that (2) had received systemic treatment immediately at presentation, corticosteroids alone, or dual steroidal and non-steroidal immunosuppressants, and (3) contained clear information on the evolution of the disease, chronic evolution, and/or sunset-glow fundus (SGF) versus absence of chronic disease and/or absence of SGF.

Because the distinction between initial-onset VKH and chronic VKH was not made in most studies in the past, the number of studies that could be included were strikingly few. Sixteen studies were identified that reported treatments using systemic corticosteroids alone [Table 1]. Of these studies, 11/16 (69%) were performed before 2015. Four studies reported treatments combining steroidal and non-steroidal immunosuppression which were all performed after 2011 (1 study in 2011, 2 in 2017 and 1 in 2018) [Table 2]. With time, the proportion of studies using dual immunosuppressive treatments increased, 1/11 before 2015 versus 3/5 after 2015.

Table 1 lists the 16 studies of initial-onset VKH patients treated with systemic corticosteroids as unique systemic treatment. The total number of initial-onset VKH patients treated with systemic corticosteroids as unique systemic treatment amounted to 802. To establish the proportion of chronic evolution, 700 patients were available for analysis, of which 306 (44%) had a chronic course that could not be avoided by corticosteroid treatment alone. To establish the proportion of cases that developed SGF, 391 patients were available from 6 studies where this complication was reported. A total of 230/391 (59%) patients developed SGF when corticosteroid treatment was given alone, indicating smoldering progression of choroiditis.

Table 2 lists the four studies of initial-onset acute VKH patients treated with a combination of steroidal and non-steroidal immunosuppression immediately at presentation. The result of these studies showed that chronic evolution was reduced from 44% to 2.3%, a highly statistically significant difference (\(P<0.000001\), Fisher’s exact test). In 3 studies comprising 148 patients, chronic evolution was reduced to zero altogether. SGF was reduced from 59% in the corticosteroid-alone group to 17.5%, a highly statistically significant difference (\(P<0.00001\), Fisher’s exact test). The different regimens of non-steroidal immunosuppressants used are indicated in the table 2.

**DISCUSSION**

The appraisal of VKH disease has been inadequate in the past because it failed to distinguish between two stages of the disease, initial-onset disease and chronic disease, corresponding to different evolutions and to different responses to management.\(^16\) The modality of management of initial-onset VKH disease is still debated. On one side, a substantial number of clinicians, centers, and even countries claim that systemic corticosteroid therapy is sufficient to manage the disease.\(^29\) On the other hand, in recent years, there is an increasing trend, based on reports, some of them conducted in a prospective
Table 1: Studies reporting on results of corticosteroid monotherapy in patients presenting with initial-onset Vogt-Koyanagi-Harada disease

| Author                        | Country   | Year | Number of patients | Treatment | Number of patients with chronicity (%) | Number of patients with SGF (%) |
|-------------------------------|-----------|------|--------------------|-----------|----------------------------------------|-------------------------------|
| Rubsamgen and Gass\(^{15}\)  | USA       | 1991 | 19                 | CS        | 19 (100)                               | N/A                           |
| Nishioka et al.\(^{16}\)     | Japan     | 1995 | 87                 | CS        | 29 (33)                                | N/A                           |
| Keino et al.\(^{17}\)        | Japan     | 2002 | 80                 | CS        | 14 (18)                                | 54 (68)                       |
| Keino et al.\(^{18}\)        | Japan     | 2006 | 102                | CS        | N/A                                    | 69 (68)                       |
| Tugal-Tutkun et al.\(^{19}\) | Turkey    | 2007 | 19                 | CS        | 18 (95)                                | 14 (74)                       |
| Khairallah et al.\(^{20}\)   | Tunisia   | 2007 | 38                 | CS        | 23 (61)                                | N/A                           |
| Chee et al.\(^{21}\)         | Singapore | 2007 | 39                 | CS        | 18 (49)                                | N/A                           |
| Lai et al.\(^{22}\)          | Hong-Kong | 2009 | 35                 | CS        | 12 (34)                                | 18 (51)                       |
| Cuchacovich et al.\(^{23}\)  | Chile     | 2010 | 44                 | CS        | 21 (48)                                | N/A                           |
| Errera et al.\(^{24}\)       | France    | 2011 | 42                 | CS        | 31 (73)                                | N/A                           |
| Abu El-Asrar et al.\(^{25}\) | Saudi Arabia | 2013 | 28                 | CS        | 19 (68)                                | 13 (46)                       |
| Ozdal et al.\(^{26}\)        | Turkey    | 2014 | 16                 | CS        | 7 (44)                                 | 7 (44)                        |
| Iwahashi et al.\(^{27}\)     | Japan     | 2015 | 55                 | CS        | 14 (26)                                | N/A                           |
| Sakata et al.\(^{28}\)       | Brazil    | 2015 | 29                 | CS        | 23 (79)                                | N/A                           |
| Giordano et al.\(^{29}\)     | Argentina | 2017 | 58                 | CS        | 33 (57)                                | N/A                           |
| Nakayama et al.\(^{29}\)     | Japan     | 2019 | 111                | CS        | 25 (23)                                | 55 (50)                       |
| Total                         |           | 802  | CS                 |           | 306/700=44%                           | 230/391=59%                   |

SGF: Sunset-glow fundus, VKH: Vogt-Koyanagi-Harada, CS: Corticosteroid, N/A: Not available

Table 2: Studies reporting on results of dual corticosteroid and non-steroidal treatment in patients presenting with initial-onset Vogt-Koyanagi-Harada disease

| Author                        | Year | Number of patients | Treatment | Number of patients with chronicity (%) | Number of patients with SGF (%) |
|-------------------------------|------|--------------------|-----------|----------------------------------------|-------------------------------|
| Bouchenaki and Herbourt\(^{30}\) | 2011 | 5                  | CS+IST    | 0 (0)                                  | 0 (0)                         |
| Abu El-Asrar et al.\(^{31}\)  | 2017 | 38                 | CS+MMF    | 0 (0)                                  | 0 (0)                         |
| Lodhi et al.\(^{32}\)         | 2017 | 24                 | CS+AZA    | 4 (17)                                 | 6 (25)                        |
| Yang et al.\(^{33}\)          | 2018 | 105                | CS+IST    | 0 (0)                                  | 24 (23)                       |
| Total                         | 172  | CS+IST             | 4/172=2.3%| 30/172=17.5%                          |                               |

SGF: Sunset-glow fundus, CS: Corticosteroid, IST: Diverse conventional and validated immunosuppressive treatments, MMF: Mycophenolate Mofetil, AZA: Azathioprine

With the increasing use of OCT and ICGA, the disease cure can be expected for this autoimmune disease can be explained by the particular clinicopathology of the disease. VKH is developing in the confined space of the eye and more precisely in the choroidal stroma. Early and aggressive immunosuppressive therapy will then avoid remnant epitope generation in an autoimmune process that is not fully matured and moreover takes place in secluded compartment which the eye is. The first inflammatory event is a stromal choroiditis and in case rapid and aggressive treatment does not confine back the inflammation to its original focus, it will propagate to adjacent eye structures, the optic disc and retina, will spread to be prolonged. One study also showed that monitoring of occult subclinical choroidal inflammation using ICGA resulted in the cure of the disease after a treatment duration of 27 months with no recurrence after a treatment-free follow-up period of 26 months. It has been shown that ICGA is the most sensitive modality to follow choroidal involvement in VKH, but enhanced depth imaging OCT is another modality that can be used if ICGA is unavailable. The fact that a disease cure can be expected for this autoimmune disease can be explained by the particular clinicopathology of the disease. VKH is developing in the confined space of the eye and more precisely in the choroidal stroma. Early and aggressive immunosuppressive therapy will then avoid remnant epitope generation in an autoimmune process that is not fully matured and moreover takes place in secluded compartment which the eye.
anteriorly to become a (granulomatous) panuveitis and will produce ear lesions and integumentary manifestations. This natural evolution of the disease was described in detail by the ground-breaking work of Koyanagi in 1929.37

Another positive consequence of combined immunosuppressive therapy is the considerable corticosteroid-sparing effect it allows to achieve, as substantially less corticosteroids can be given and consequently their deleterious morbidity can be reduced.

In uveitis and immunogenic inflammatory diseases as a whole the present trend is towards the use of less corticosteroids and more non-steroidal immunosuppression. For VKH such a radical approach has a double advantage. In addition to potent direct inflammation suppressive action, it contributes to the rapid restoratuation of the blood-ocular barriers, recreating the secluded ocular cocoon, making the cure of the disease possible. Today, we dispose of a large array of immunosuppressive agents which we manipulate more appropriately. When considering the severity of side effects between corticosteroids and conventional immunosuppressants such as mycophenolic acid, azathioprine, or cyclosporine, the balance clearly leans favorably toward the latter and this is even more the case with biologic agents.38–40 Taking into account the low proportion of side effects of non-steroidal immunosuppressants and their corticosteroid sparing effect, the benefits largely exceed the inconveniences of their use, when knowing that close to half of initial-onset VKH will be preserved from chronic evolution. When considering SGF, an indicator of ongoing smoldering choroiditis, the benefits are even higher as only 17.5% versus 60% will develop SGF when on combined therapy.41,42

In summary, this study including close to one thousand patients clearly showed in a statistically significant fashion that combined steroidal and non-steroidal immunosuppression for VKH disease is effective and safe and allows to achieve, as substantially less corticosteroids can be given and consequently their deleterious morbidity can be reduced.

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Conflicts of interest
There are no conflicts of interest.

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In summary, this study including close to one thousand patients clearly showed in a statistically significant fashion that combined steroidal and non-steroidal immunosuppression can prevent both chronic evolution and SGF after initial-onset VKH disease.
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