New Perspectives on the Immunopathogenesis and Treatment of Uveitis Associated With Vogt-Koyanagi-Harada Disease

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Uveitis associated with Vogt-Koyanagi-Harada (VKH) disease is a bilateral, chronic, granulomatous autoimmune disease associated with vitiligo, poliosis, alopecia, and meningeal and auditory manifestations. The disease affects pigmented races with a predisposing genetic background. Evidence has been provided that the clinical manifestations are caused by a T-lymphocyte-mediated autoimmune response directed against antigens associated with melanocytes in the target organs. Alongside of T lymphocytes, autoreactive B cells play a central role in the development and propagation of several autoimmune diseases. The potential role of B lymphocytes in the pathogenesis of granulomatous uveitis associated with VKH disease is exemplified within several studies. The early initial-onset acute uveitic phase typically exhibits granulomatous choroiditis with secondary exudative retinal detachment and optic disc hyperemia and swelling, subsequently involving the anterior segment if not adequately treated. The disease eventually progresses to chronic recurrent granulomatous anterior uveitis with progressive posterior segment depigmentation resulting in “sunset glow fundus” appearance and chorioretinal atrophy if not properly controlled. Chronically evolving disease is more refractory to treatment and, consequently, vision-threatening complications have been recognized to occur in the chronic recurrent phase of the disease. Conventional treatment with early high-dose systemic corticosteroids is not sufficient to prevent chronic evolution. Addition of immunomodulatory therapy with mycophenolate mofetil as first-line therapy combined with systemic corticosteroids in patients with acute initial-onset disease prevents progression to chronic evolution, late complications, vitiligo, and poliosis. Furthermore, patients under such combined therapy were able to discontinue treatment without relapse of inflammation. These findings suggest that there is a therapeutic window of opportunity for highly successful treatment during the early initial-onset acute uveitic phases, likely because the underlying disease process is not fully matured. It is hypothesized that early and aggressive immunosuppressive therapy will prevent remnant epitope generation in the initiation of the autoimmune process, the so-called primary response. B cell depleting therapy with the
anti-CD20 monoclonal antibody rituximab is effective in patients with refractory chronic recurrent granulomatous uveitis. The good response after rituximab therapy reinforces the idea of an important role of B cells in the pathogenesis or progression of chronic recurrent uveitis associated with VKH disease.

Keywords: autoimmune disease, B cells, immunomodulatory therapy, therapeutic window of opportunity, remnant epitope, molecular mimicry

INTRODUCTION

Vogt-Koyanagi-Harada (VKH) disease is a multisystem T-lymphocyte-mediated autoimmune disease directed against antigens associated with melanocytes present in the target organs including the uvea, inner ear, meninges, and integumentary system. Several studies demonstrated that tyrosinase family proteins are important antigens specific to VKH disease (1–3). Patients with VKH disease show different clinical manifestations depending on the duration of the disease before presentation. Patients with initial-onset acute uveitis present with granulomatous choroiditis with secondary exudative retinal detachment resulting from impairment of the retinal pigment epithelium caused by choroidal inflammation with typical optic nerve head swelling and hyperemia (Figure 1). During the acute uveitic phase, compression of the vessels by edema and granulomatous inflammation interferes with choroidal blood flow and induces choroidal circulation impairment. Laser speckle flowgraphy studies demonstrated inflammation-related impairment of choroidal and optic nerve head blood flow velocity in patients with acute uveitis associated with VKH disease. Systemic immunosuppressive therapy improved inflammation-related impairment in blood flow velocity (4). These circulatory disturbances may cause axonal flow stasis and secondary axonal swelling of the optic nerve head (5). The inflammation subsequently involves the anterior segment if not adequately treated. The disease will proceed to chronic recurrent granulomatous anterior uveitis if not properly controlled (6–8). Progressive subclinical choroidal inflammation due to inadequate immunosuppression in the initial-onset acute uveitic phase will lead to progressive posterior segment depigmentation resulting in “sunset glow fundus” appearance and chorioretinal atrophy (Figure 2) (9–11). During the acute phase, systemic manifestations include neurological and auditory signs. Neurological manifestations include meningismus (headache and stiffness of the neck and back) with cerebrospinal fluid (CSF) lymphocytic pleocytosis. It is presumed that pleocytosis is caused by cell-mediated immunoreaction against melanocytes in the meninges (12). The audiovestibular symptoms include sensorineural hearing loss, tinnitus, and vertigo. In the chronic recurrent phase, integumentary manifestations (poliosis, vitiligo, and alopecia) may develop. The disease affects pigmented races and individuals of certain genetic predisposition (13). HLA-DR4 and HLA-DRW53, with the most significant risk allele being HLA-DRB1*0405, were found to be genetically associated with VKH disease (7).

Patients with chronic recurrent disease manifest more severe granulomatous inflammation of the anterior segment at presentation. In addition, final visual acuity and mean retinal sensitivity are worse in chronic recurrent disease compared with initial-onset acute disease (8, 14). Studies using laser flare-cell meter demonstrated that both aqueous flare values and cell counts were significantly higher in chronic recurrent disease than those in initial-onset acute disease. Moreover, chronic recurrent granulomatous inflammation is more refractory to treatment, needing prolonged and repeated therapeutic interventions (15). Therefore, vision-threatening complications including glaucoma, cataract, subretinal fibrosis, chorioretinal atrophy, choroidal neovascular membranes, and “sunset glow fundus,” are more common in chronic recurrent disease (6, 8, 9). Indocyanine green angiographic studies of patients during episodes of apparent isolated granulomatous anterior segment recurrence demonstrated choroidal involvement suggesting ongoing subclinical choroidal inflammation despite the absence of clinical signs of posterior segment inflammation (16). Histopathologic studies of eyes with “sunset glow fundus” revealed the presence of scattered inflammatory infiltrates in the thickened choroid with disappearance of choroidal melanocytes (17). These 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 (16–19). Therefore, the main goals in the treatment of the acute uveitic phase are to suppress the uveal inflammation in the acute posterior uveitis stage with adequate immunosuppressive therapy and prevention of the progression to chronic recurrent evolution.

This article aims to provide new insights on the immunopathogenesis and to open perspectives for treatment of uveitis associated with VKH disease.

DEFINING THE THERAPEUTIC WINDOW OF OPPORTUNITY IN INITIAL-ONSET ACUTE UVEITIS ASSOCIATED WITH VKH DISEASE

A therapeutic window of opportunity is a well-established concept of critical importance in rheumatoid arthritis clinical research and considerable attention has been paid to when it might close. This window represents a very early phase of the disease in which therapeutic disease modification is more successful, presumably because of a not fully matured underlying disease process (20). A growing body of evidence has emphasized the consistent clinical and radiographic benefits of prompt initiation of disease-modifying antirheumatic drugs in patients...
with rheumatoid arthritis during early stages of the disease. Therapeutic intervention in this period alters the natural history of the disease and hampers disease progression in such a way that chronicity is reduced. These findings have led to changes in rheumatoid arthritis treatment paradigms, with increasing emphasis on early diagnosis and treatment (21, 22).

In a prospective study, it was demonstrated that none of the patients who presented early with initial-onset acute VKH disease without anterior segment inflammation progressed to chronic recurrent disease or developed any complication of cataract or glaucoma or subretinal neovascular membranes or “sunset glow fundus” or chorioretinal atrophy during the follow-up period. In contrast, 16.4 and 13.6% of the patients with initial-onset acute VKH disease with anterior segment inflammation due to delayed patient presentation developed glaucoma and cataract, respectively, during the follow-up period (9). Such findings are suggestive for a need of prompt diagnosis and therapy without delay in the very early phases of acute VKH disease. It seems that prompt and adequate treatment before the occurrence of anterior segment inflammation is essential to prevent the development of complications. In a similar way to rheumatoid arthritis, catching this therapeutic window of opportunity in the very early phases of acute uveitis associated with VKH disease prevents progression to chronic recurrent evolution and development of complications and “sunset glow fundus.” This window represents a very early disease phase in which therapeutic disease modification is more successful, likely because the underlying disease process is not fully matured (20–22).

**SYSTEMIC CORTICOSTEROID MONOTHERAPY IS NOT EFFECTIVE IN PREVENTING CHRONIC RECURRENT EVOLUTION AND DEVELOPMENT OF COMPLICATIONS AND “SUNSET GLOW FUNDUS”**

Early diagnosis, timely initiation of immunosuppressive therapy and appropriate and adequate treatment are key to the optimal management of uveitis associated with VKH disease. A delay in diagnosis and in initiating adequate treatment are associated with a high risk of developing disease chronicity, complications and visual impairment (23).

Increasing evidence suggests that, despite proper treatment with corticosteroid monotherapy, many patients progress to chronic recurrent granulomatous inflammation and develop “sunset glow fundus” and chorioretinal atrophy even after the clinical disease appears to be under control (23). Keino et al. (24) retrospectively studied 80 patients with VKH disease treated with high-dose systemic corticosteroid therapy from initial-onset. Chronic ocular inflammation developed in 17.5% of patients, and “sunset glow fundus” developed in 67.5% of these patients. In another study, Keino et al. (25) reviewed the charts of 102 patients with VKH disease who were treated with high-dose systemic corticosteroid therapy at initial onset. “Sunset glow fundus” was observed in 67.6% of these patients. The mean duration until the appearance of “sunset glow fundus” was 4.2 ± 2.7 months.
Chee et al. (26) observed that one-third of patients receiving high-dose systemic corticosteroid therapy within 2 weeks of presenting with symptoms progressed to chronic recurrent disease. Tugal-Tutkun et al. (27) observed that 95% of patients who presented in the acute uveitic phase progressed to chronic recurrent evolution. Lai et al. (18) demonstrated the development of “sunset glow fundus” in 51.4% of patients who received systemic corticosteroids during the first attack of VKH disease. Sakata et al. (28) demonstrated that despite early high-dose systemic corticosteroid therapy within 30 days from disease onset and a slow taper, 79% of patients with VKH disease progressed to chronic recurrent evolution, and 38% developed subretinal fibrosis. Recently, Nakayama et al. (29) demonstrated that despite high-dose corticosteroid therapy in patients with new-onset acute VKH disease, recurrent inflammation was observed in 22.5% of patients. In this cohort, “sunset glow fundus” developed in 49.5% of eyes and ocular complications were observed in 21.2% of eyes.

**IMMUNOMODULATORY THERAPY AS FIRST-LINE TREATMENT COMBINED WITH SYSTEMIC CORTICOSTEROIDS IN INITIAL-ONSET ACUTE UVEITIS ASSOCIATED WITH VKH DISEASE PREVENTS CHRONIC RECURRENT EVOLUTION AND CURES THE DISEASE**

Because of the poor prognosis associated with chronic recurrent evolution and the well-documented complications of long-term high-dose corticosteroid treatment, several retrospective studies suggested to initiate non-steroidal immunomodulatory therapy in addition to systemic corticosteroids early in the course of the disease to achieve better control of the uveitis and to facilitate earlier tapering of corticosteroids (7, 8, 30–32). In prospective studies, addition of immunomodulatory therapy with mycophenolate mofetil as first-line therapy combined with systemic corticosteroids in patients with initial-onset acute uveitis associated with VKH disease prevented the progression of the disease to chronic recurrent evolution and development of complications and “sunset glow fundus.” Furthermore, mycophenolate mofetil was effective in preventing the development of vitiligo, poliosis, alopecia and sensory hearing loss (10, 11). These findings suggest that mycophenolate mofetil was effective in controlling progressive subclinical choroidal inflammation. Therefore, uveal depigmentation and chorioretinal atrophy should not be regarded as signs of convalescence. Rather, we suggest that they be considered signs of ongoing subclinical choroidal inflammation due to inadequate immunosuppressive therapy. One of the most important goals in using non-steroidal immunomodulatory treatment in non-infectious uveitis is to minimize exposure to corticosteroids and to reduce corticosteroid levels. In our study, a corticosteroid-sparing effect (prednisone dose ≤ 10 mg/day) was achieved in all patients after a mean time of 3.8 ± 1.3 months. Furthermore, patients were able to discontinue treatment without relapse of inflammation (Figure 1) (11).

These findings suggest that, similar to rheumatoid arthritis, there is a therapeutic window of opportunity for highly successful treatment of uveitis associated with VKH disease during the very early acute uveitic phase, likely because the underlying disease process is not fully matured (20–23). Treatment with mycophenolate mofetil as first-line therapy combined with systemic corticosteroids during the therapeutic window is able to modify the phenotype of VKH disease and leads to substantial improvement of disease outcome avoiding chronic evolution, “sunset glow fundus,” late complications, vitiligo, poliosis, alopecia, and sensory hearing loss and it achieved cure of disease after discontinuation of treatment.

Recently, Lin Oo et al. (33) showed that despite introducing immunodulatory therapy with azathioprine in most of the patients within the first 3 months of onset of VKH disease combined with systemic corticosteroids, chronic evolution occurred in 51.7% of the eyes and “sunset glow fundus” developed in 58.6% of the eyes. They suggested that timing of initiation of immunomodulatory therapy is a key factor for success of treatment as immunomodulatory therapy does not take effect immediately, often taking months to have maximal effect. They too, therefore, recommended introducing immunomodulatory therapy as first-line therapy combined with systemic corticosteroids rather than when the dose of corticosteroids has been decreased.

**VKH DISEASE IS A PROTOTYPIC EXAMPLE OF AUTOIMMUNE DISEASE**

To distinguish autoimmune from (auto)inflammatory diseases clear definitions and criteria are applicable and these relate to (i) the characterization of specific autoantigens, (ii) a chronic disease course, and (iii) the involvement of adaptive immune
cells and molecules, namely T and B lymphocytes with their antigen-specific T cell receptors and antibodies (20). The classical two-signal paradigm for adaptive immune activation against infections entails the antigenic stimulus as "signal 1" and additional molecules, mainly cell adhesion molecules and cytokines as "signal 2" and this provides an immune activation mode when needed and represents a safeguard against autoimmunity (34). From a mechanistic point of view, in autoimmune diseases this "signal 1" is an autoantigen and an infection or an inflammation constitute the environmental condition for induction of the necessary cytokines and adhesion molecules to provide "signal 2." These aspects may be recapitulated by the development of preclinical animal models, that not only help to understand the immunopathogenesis but also to study therapeutic options. Refined techniques to analyze human genetic details and immune repertoires assist in better diagnosis, susceptibility profiling, prognosis and therapy of VKH disease patients. VKH disease is a true autoimmune disease with primarily tyrosinase and tyrosinase-related protein-1 and −2 (TRP-1, TRP-2) being known autoantigens in humans (1) and rats (2). At some point in ontogeny, a trigger leads to activation of specific subsets of T lymphocytes. Most probably, pro-inflammatory Th1 and Th17 cells are triggered by antigens presented within the context of major histocompatibility complex (MHC) class II (HLA-DRB1*04:05). The latter HLA class II antigen is known as an important genetic susceptibility factor in VKH disease (7, 35). Melanocyte-specific peptides have been identified as autoantigenic "signal 1" with the use of functional epitope scanning analysis (36).

Future crystallography and cryo-electron microscopy studies may elucidate how autoimmune host peptides are presented in HLA-DRB1*04:05 and how these structural details ensure the interaction with and activation of T cells with a specific T cell receptor. Although the identification of VKH disease-related autoantigens by T cell epitope scanning in individual patients characterizes these persons as having an autoimmune disease, clinical cases exist in which the presence of the above-mentioned autoantigens was difficult to prove (37). Therefore, it remains possible that additional autoantigens for activation of T cells are at play to induce cytotoxicity by CD8-positive T cells or CD4-positive helper cell activities for autoantibody induction. Alternatively, stimulation of specific B lymphocytes from the primary repertoire as immunogenic "signal 1" in the presence of an infection, e.g., by a herpes virus, as signal 2 for helper activity induction as bystander effect, may lead to autoantibody formation (vide infra). Both antibodies and autoreactive T cells against autoantigens cause autoimmune-related cytotoxicity and tissue damage.

Caution and a critical attitude about causal inference remain necessary about infections as triggers for VKH disease (38). Virus infections, including Hepatitis B (39), Hepatitis C virus under interferon therapy (40), cytomegalovirus (CMV) and other herpesviruses (38, 41) have all been associated with VKH disease. Efforts to corroborate the latter findings failed so far and the ensemble of such studies cautions that an association does not necessarily represent a cause (42). In this respect, the type of body fluid analyzed (vitreous vs. cerebrospinal fluid) may be critical to detect the presence of viruses, as it is known that even in single patients different strains of viruses may be compartmentalized at specific locations (37, 43).

Virus infections may provide direct or indirect triggers to initiate or perpetuate VKH disease at least in two different ways. First and as hypothesized by the molecular mimicry paradigm (44), linear or conformational viral protein antigens from e.g., CMV may cross-react with tyrosinase peptides in T cell activation tests (45). Secondly and as hypothesized by the remnant epitope paradigm (20) extracellular inflammatory proteolysis, associated with various types of viral or bacterial infections, may locally lead to degradation of melanocyte proteins into remnant epitopes. On a statistical basis (cleavage sites, abundance class) the generated autoantigenic peptides enhance the chance of (re)activation of autoreactive T or B lymphocytes. In both paradigms, molecular mimicry and remnant epitopes, the two necessary signals for T cell activation (remnant epitope or viral antigen as signal 1 and the infectious/inflammatory context as signal 2) are both simultaneously present (Figure 3). So far, it is easier to understand how the two mechanisms of mimicry and remnant epitopes play a role in the reactivation than in the initiation of VKH disease. It is also conceivable that both paradigms are at play together in the autoimmune initiation process. In view of observed frequencies of occurrence of autoimmune diseases, it is plausible that remnant epitopes (associated with various types of infectious agents) are more common than molecular mimicry (associated with a single infection). Finally, it may be questioned how intracellular molecules, such as tyrosinase or TRP-1 and TRP-2, may be cleaved by extracellular proteases to yield immunogenic remnant epitopes in the autoimmune process of VKH disease. Various processes leading to different types of cytolysis may be invoked when infections and collateral cell and tissue damage develop. For instance, punctuate lesions observed in VKH patients in vivo and named mutton-fat granulomatous keratic precipitates (as visualized in Figure 2) are reminiscent of a virus plaque assay in vitro and may indicate spots where cytolysis occurs, either by the direct cytopathogenic effect of a virus or by various types of indirectly induced forms of immune-mediated cytotoxicity. For instance, the classical activation pathway of the complement system by immune complexes or the action of cytotoxic T lymphocytes or natural killer cells may lead to host cell cytolysis. As an additional possibility, also intracellular proteases, such as caspases, may generate remnant epitopes from intracellular substrates, such as tyrosinase and TRP-1 and −2 and these may become accessible for antigen presentation to T cells and for B lymphocytes when the host cell disintegrates, e.g., by apoptosis.

B LYMPHOCYTES IN THE PATHOGENESIS OF GRANULOMATOUS UVEITIS ASSOCIATED WITH VKH DISEASE

Analysis of the aqueous humor samples from patients with uveitis may help in generating novel biomarkers for different phenotypes of uveitis. This type of information may be helpful for better diagnosis and to improve treatment by better
stratification of patients. Currently, a commonly used approach to enhance specificity and selectivity for diagnostic purposes is to combine various markers. Aside this, the discovery of pathogenic biomarkers is preferred, notwithstanding that it may be more laborious. Only after the causal role of specific molecules for particular disease entities is established, these may serve as potential targets for selective therapy.

Toward the aim of finding pathogenic biomarkers for various clinical entities of uveitis, aqueous humor samples from patients with active uveitis associated with Behçet’s disease, sarcoidosis, HLA-B27-related intraocular inflammation and VKH disease were compared for the presence of chemokines, cytokines and soluble cytokine receptors (46–51). Results of pairwise comparisons are shown in Table 1. Although for VKH disease the number of possible biomarkers was frustratingly low; two stood out as possibly relevant and both were related to B cell biology: CXCL13 and the tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) (46–51).

CXCL13 was originally identified as B cell attracting chemokine 1 (52), expressed in lymph follicles and in the liver, spleen, and gut. It assists in the homing of B lymphocytes to these sites via its receptor CXCR5, originally named Burkitt’s lymphoma receptor-1 (53). Related to autoimmunity, several complementary studies demonstrated that CXCL13 is an important mediator of human autoimmune disorders, such as rheumatoid arthritis (54, 55), systemic lupus erythematosus (56, 57), multiple sclerosis (58, 59) and myasthenia gravis (60). CXCL13 levels were upregulated in synovial tissue (54) and plasma (55) from patients with rheumatoid arthritis, in serum (56) and plasma (57) from patients with systemic lupus erythematosus, in CSF from patients with multiple sclerosis (58, 59) and in serum from patients with myasthenia gravis (60). These studies identified CXCL13 to be a useful inflammatory biomarker (54–60). CXCL13 neutralizing monoclonal antibody significantly reduced disease severity in animal models of rheumatoid arthritis and experimental autoimmune encephalomyelitis (61).

The levels of the B cell chemoattractant CXCL13 in aqueous humor samples from patients with uveitis associated with VKH disease largely exceeded those in patients with Behçet’s disease or HLA-B27-associated uveitis (46, 47). In these studies, the concentrations of CXCL13 in the aqueous humor samples were quantified in two sets of aqueous humor samples with the use of two multiplex assays (46, 47). The levels of CXCL13 were elevated 1423.6-fold in VKH disease, 298.3-fold in Behçet’s disease, 107.1-fold in HLA-B27-associated uveitis and 458.2-fold in sarcoidosis compared to controls (47). CXCL13 levels in VKH disease were significantly higher than the levels in Behçet’s disease and
TABLE 1 | Summary of pairwise comparisons between disease groups.

I. CXC chemokines
A. Neutrophil chemoattractants
- Growth-related oncogene (GRO)-α/CXCL1
  - BD > VKH, sarcoidosis
  - HLA-B27 > VKH, sarcoidosis
- GRO-β/CXCL2
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
- Epithelial-derived neutrophil attractant-78 (ENA-78)/CXCL5
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
- Granulocyte chemotactic protein-2 (GCP-2)/CXCL6
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
- Interleukin-8 (IL-8)/CXCL8
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
B. T helper-1 (Th1) lymphocyte chemoattractants
- Interferon-γ-inducible protein of 10 kDa (IP-10)/CXCL10
  - BD > VKH

C. Lymphoid chemokines
- B cell attracting chemokine-1 (BCA-1)/CXCL13
  - VKH, sarcoidosis > BD
  - VKH > HLA-B27

II. Soluble form of transmembrane chemokines (Preferentially act on Th1 lymphocytes)
- Scavenger receptor for phosphatidyl serine and oxidized low-density lipoprotein (SR-PSOX)/CXCL16
  - BD > VKH, sarcoidosis
  - HLA-B27 > VKH, sarcoidosis
- Fractalkine/CX3CL1
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
  - Sarcoaidosis > VKH

III. CC chemokines
- Monocyte chemotactic protein (MCP)-1/CCL2
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
- MCP-3/CCL7
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
- MCP-2/CCL8
  - BD, HLA-B27 > sarcoidosis
  - HLA-B27 > VKH
- MCP-4/CCL13
  - HLA-B27 > VKH, sarcoidosis
- Thymus- and activation-related chemokine (TARC)/CCL17
  - HLA-B27 > VKH
- Macrophage inflammatory protein (MIP)-3α/CCL20
  - BD > VKH
  - HLA-B27 > BD, VKH, sarcoidosis

IV. Cytokines and soluble cytokine receptors
- Interferon-γ
  - BD > VKH
  - HLA-B27 > VKH, sarcoidosis
- Tumor necrosis factor-α (TNF-α)
  - HLA-B27 > VKH
- Interleukin (IL)-1β
  - BD > VKH
  - HLA-B27 > BD, VKH, sarcoidosis
- IL-6
  - BD > VKH, sarcoidosis
  - HLA-B27 > VKH, sarcoidosis
- IL-11
  - HLA-B27 > VKH, sarcoidosis
- IL-12p40
  - BD > VKH
  - HLA-B27 > VKH
- IL-19
  - HLA-B27 > BD, VKH, sarcoidosis
- IL-35
  - HLA-B27 > VKH, sarcoidosis
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)
  - HLA-B27 > VKH, sarcoidosis
- The TNF-like weak inducer of apoptosis (TWEAK)
  - VKH > HLA-B27
  - Sarcoidosis > BD, HLA-B27
- Soluble (s) CD30
  - VKH > BD, HLA-B27

BD, Behçet’s disease; HLA-B27, HLA-B27-associated uveitis; VKH, Vogt-Koyanagi-Harada disease.

(Continued)
suggest that B lymphocytes may be pathogenically important in granulomatous uveitis associated with VKH disease and that pathogenic B cell depletion might be effective in patients with refractory granulomatous uveitis associated with VKH disease.

The original finding of autoantibodies against host antigens and the formation of pathogenic immune complexes (20) has been reinforced with interventional studies, providing increasing evidence that B lymphocytes play an important role in the pathogenesis of autoimmune diseases, such as myasthenia gravis, autoimmune thyroiditis, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus (66–69). In addition to producing autoantibodies, B cells may capture antigens through their B cell receptors and contribute to autoimmunity by presenting autoantigens to pathogenic T cells providing T cell help, production of pro-inflammatory cytokines and formation of tertiary lymphoid structures, a process termed neo-organogenesis. Consequently, B cell-targeted therapies have emerged as an effective therapy in patients with autoimmune diseases even in diseases that are believed to be mainly mediated by T cells, such as rheumatoid arthritis and multiple sclerosis (66–69).

**EFFICACY OF B CELL DEPLETING THERAPY WITH RITUXIMAB IN REFRACTORY CHRONIC RECURRENT UVEITIS ASSOCIATED WITH VKH DISEASE**

Rituximab is a chimeric mouse/human monoclonal antibody against the pan B cell marker CD20. CD20 is a transmembrane protein expressed on naive and memory B cells, but not on stem cells or fully differentiated plasma cells. Rituximab has emerged as an effective therapy in patients with autoimmune diseases refractory to conventional immunosuppression, with the rationale of depleting pathogenic B cells (66–69). The efficacy of anti-CD20-mediated B cell depletion in treating autoimmune diseases supports an important role for B cells in the development and propagation of these diseases.

Rituximab was reported to be effective in three individual cases of resistant uveitis associated with VKH disease (70–72). We presented the first series and long-term follow-up study of 9 patients with refractory chronic recurrent granulomatous uveitis associated with VKH disease treated with rituximab. All patients were resistant to conventional immunosuppressive therapy and TNF-α blockers. In this group of patients, rituximab made a significant contribution to control inflammation. Adjuvant rituximab allowed the daily immunosuppressive doses to be reduced (73). Similarly, Bolletta et al. (74) demonstrated the efficacy of rituximab therapy in 5 patients with refractory uveitis associated with VKH disease. The good response after rituximab therapy suggests an important role of B cells in the pathogenesis of chronic recurrent uveitis associated with VKH disease.

**CONCLUSIONS**

In conclusion, VKH disease is a true autoimmune disorder that has become an example in the field with the demonstration that the combination of research efforts in basic immunology, the use of preclinical animal models and critical attitudes to association and clinical case report studies leads to the cure of initial-onset acute VKH disease, possible by preventing autoimmunization. In addition, for VKH patients who have progressed into chronic disease, treatment with rituximab to control the damage caused by autoantibodies and by B lymphocytes acting as antigen-presenting cells to pathogenic T cells, represents a therapeutic modality that needs broad attention. Both types of treatments, early aggressive immunosuppression preventing autoimmunization (20) and rituximab in progressed VKH disease are not antigen-specific. Thanks to new developments toward antigen-specific immune tolerance induction with mRNAs encoding specific autoantigens (75), we may now also be on the verge to additional progress, also for VKH disease.

**AUTHOR CONTRIBUTIONS**

AA wrote the manuscript. SS, GO, and JV critically edited the manuscript. All authors contributed to the manuscript and approved the final submission.

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