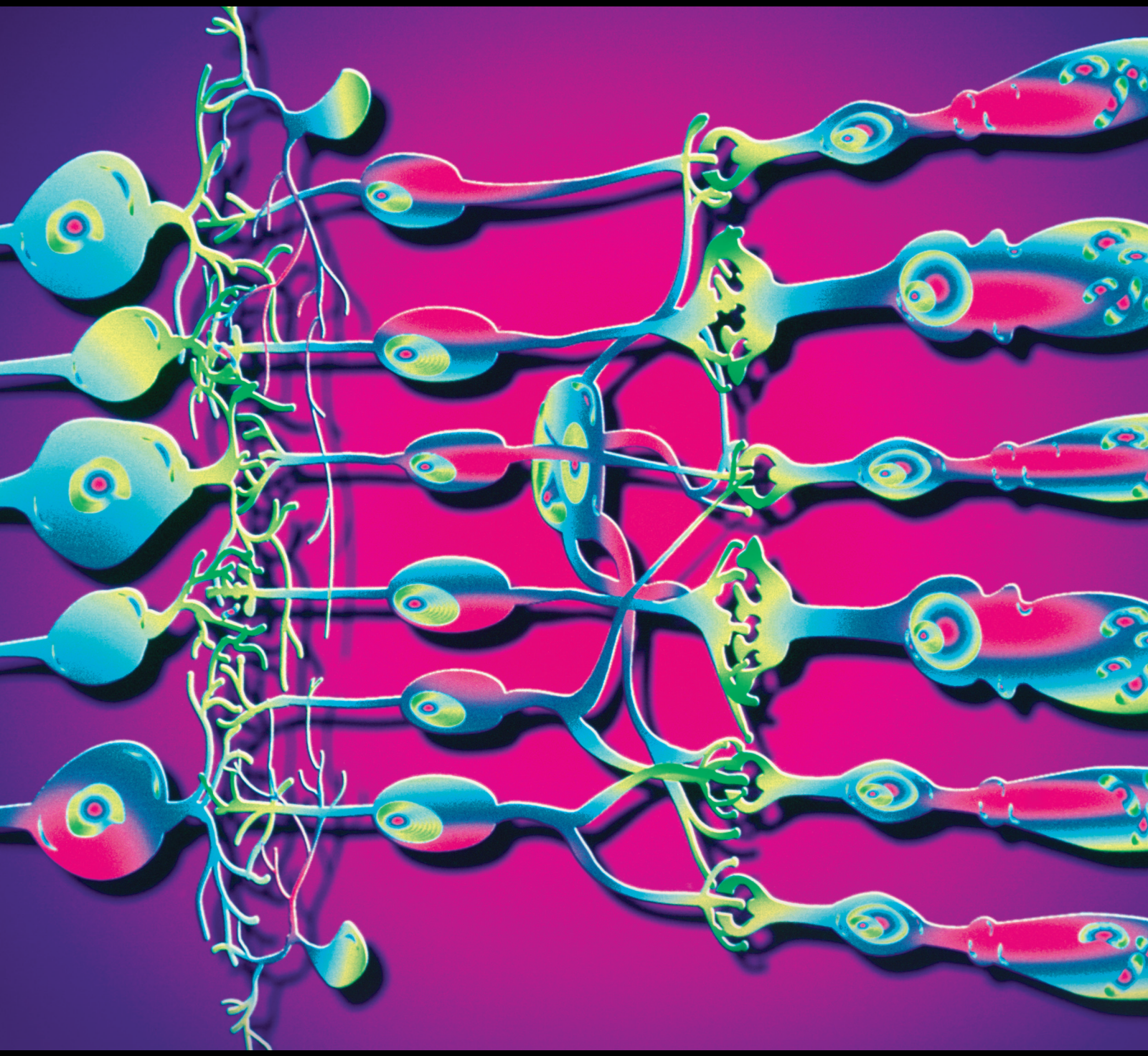
Journal of Ophthalmology

Update on Uveitis Management

Guest Editors: Vishali Gupta, Quan Dong Nguyen, Manfred Zierhut, and Ilknur Tugal-Tutkun



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Editorial Board

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Editorial

Update on Uveitis Management

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Uveitis management has made a dramatic progress in the last decade with the development of new drugs as well as the change in the approach to the patients. There are several new drugs available including biologics, recombinant monoclonal antibodies against interleukins including IL-17, IL-l, and IL-6, and anti-TNF-α and T-cell inhibitors such as fusion proteins. In addition, there has been a shift in the drug administration with the preference of local administration of therapy by using intravitreal injection or iontophoresis. The widespread use of anti-VegF agents has brought a change in the management strategies of inflammatory choroidal neovascular membranes as well as uveitic macular edema. The availability of newer imaging techniques including fundus autofluorescence (FAF) for imaging of the retinal pigment epithelium and enhanced depth imaging of the choroid by OCT too has influenced the management of uveitis by titrating the therapy for each patient.

This special issue on update in uveitis management has review articles as well as original articles addressing these issues. In a review article, "Role of Autofluorescence in Inflammatory/Infective Diseases of the Retina and Choroid," A. Samy et al. have reviewed the published literature on FAF in inflammation of the posterior segment, specifically patterns in infectious and noninfectious uveitis, and illustrated their relevance with the help of illustrations and case histories. The review by A. Baltmr et al. "Examining the Choroid in Ocular Inflammation: A Focus on Enhanced Depth Imaging" summarizes the current application of EDI technique in ocular inflammatory disorders and highlights its utility as an additional tool in monitoring choroidal involvement in ocular inflammation. In an original article, "The Effects of Intravitreal Bevacizumab in Infectious and Noninfectious Uveitic Macular Edema," H. Al-Dhibi et al. have reported the efficacy of intravitreal bevacizumab injections in the management of uveitic macular edema (UME) associated with both infectious and noninfectious uveitides. Importantly, intravitreal bevacizumab was found to induce remission of UME with no immunosuppressive effect against infectious agents. E. D'Ambrosio et al. in "Management of Uveitis-Related Choroidal Neovascularization: From the Pathogenesis to the Therapy" have reviewed the pathogenesis as well as management strategies for inflammatory choroidal neovascular membranes. L. Talat et al. in "Ischemic Retinal Vasculitis and Its Management" have reviewed the current options in the treatment of ischemic retinal vasculitis including the role of conventional as well as newer biological agents in the management of this challenging entity. Lastly, in a review by J. R. Maya et al., "Emerging Therapies for Noninfectious Uveitis: What May Be Coming to the Clinics," the authors have reviewed all the emerging therapies for the management of noninfectious uveitis addressing the curiosity and concerns about the newer therapies that shall be coming to the clinics.

We sincerely hope that the readers will find these well-selected manuscripts of interest and obtain useful information to get an update on the management of uveitis.

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Clinical Study

The Effects of Intravitreal Bevacizumab in Infectious and Noninfectious Uveitic Macular Edema

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Background/Aims. To assess the effect of intravitreal bevacizumab injection (IVBI) for the treatment of macular edema due to infectious and noninfectious uveitides. *Design.* Retrospective interventional case series. *Methods.* A chart review was performed on all the patients who were diagnosed with uveitic macular edema (UME) and received 1.25 mg of IVBI at two referral centers in Riyadh, Saudi Arabia. All included patients had their visual acuity and macular thickness analyzed at baseline and at 1 and 3 months following IVBI and any sign of reactivation was noted. *Results.* The mean age of patients was 41 ± 16 years with a mean followup of 4 ± 1 months. Ten patients had idiopathic intermediate uveitis, 9 patients had Behcet's disease, 10 had idiopathic panuveitis, and twelve patients had presumed ocular tuberculosis uveitis. Following IVBI, the mean LogMAR visual acuity improved from 0.8 ± 0.8 at baseline to 0.4 ± 0.5 at 1 month and 0.3 ± 0.5 at 3 months ($P < 0.002$, at 3 months). The mean macular thickness was 430 ± 132 μm at baseline. Following IVBI macular thickness improved to 286 ± 93 μm at 1 month and to 265 ± 88 μm at 3 months of followup ($P < 0.001$, at 3 months). *Conclusion.* Bevacizumab was effective in the management of UME associated with both infectious and noninfectious uveitides. Intravitreal bevacizumab induced remission of UME with infectious uveitis and had no immunosuppressive effect against infectious agents.

1. Introduction

Uveitic macular edema (UME) occurs in up to 33% of uveitis cases and represents the most common cause of visual loss in patients with uveitis [1, 2]. The underlying pathophysiology of macular edema in uveitis is not well understood. However, several factors may play a role in the development of the edema including inflammatory cytokines, such as interferon gamma, interleukin 2, interleukin 6, interleukin 10, tumor necrosis factor alpha, and vascular endothelial growth factor (VEGF) [3–7].

In patients with uveitis and macular edema, greater concentrations of VEGF are upregulated compared to those without UME. Additionally, VEGF significantly stimulates and increases vascular permeability [7–10].

Early medical treatment is advocated to suppress intraocular inflammation and to prevent progressive and irreversible damage to the macular photoreceptors secondary to chronic and persistent UME [4]. Current management of UME includes the use of topical nonsteroidal anti-inflammatory, oral, periocular, and intraocular injections of corticosteroids as well as oral carbonic anhydrase inhibitors, systemic somatostatin analogs, interferon alpha, mycophenolate mofetil, and VEGF inhibitors [11–20]. However, uveitic macular edema may be nonresponsive to these treatments and continue to progress despite the control of ocular inflammation.

Bevacizumab is a recombinant humanized full-length monoclonal antibody against VEGF that has been used off-label for the treatment of age-related choroidal

neovascularization (CNV) and other ocular pathologies that include UME [21–28]. Several clinical reports have described improved visual acuity and a reduction or resolution of macular edema in patients with noninfectious uveitis following intravitreal bevacizumab or ranibizumab injection as an adjunct therapy [10, 29–34]. However, the behavior and response of macular edema due to different etiologies have not been analyzed in detail. The present study aims to compare the effect of intravitreal bevacizumab in uveitic macular edema in patients with different etiologies: idiopathic intermediate uveitis, Behcet's disease, idiopathic panuveitis, and presumed ocular tuberculosis uveitis.

2. Patients and Methods

Patient charts were reviewed for cases of uveitic macular edema who had central 1.00 mm macular thickness by OCT of >250 μm and underwent intravitreal bevacizumab injection between June 2006 and June 2009 at King Khaled Eye Specialist Hospital (KKESH) and The Eye Center in Riyadh, Saudi Arabia. Four groups were included in the study: idiopathic intermediate uveitis (IIU), Behcet's disease (BD), idiopathic panuveitis (IPU), and presumed ocular tuberculosis uveitis (POTBU). The intravitreal dosage was 1.25 mg of bevacizumab (Avastin, Genentech/Roche) and repeated as required. Inclusion criteria were patients with refractory UME that was nonresponsive to topical, periocular, or intraocular injections of corticosteroids or different systemic therapy for uveitis within the previous 3 months. Patients with UME associated with epiretinal membrane or vitreomacular traction, pregnant patients, and patients who underwent cataract or intraocular surgeries during the study period were excluded. The study was approved by the IRB.

Demographic data on age and gender of the cohort were collected. The outcome measures included baseline logarithm of the minimal angle of resolution (LogMAR), visual acuity, and macular thickness. Data were collected at 1 and 3 months after intravitreal bevacizumab. The 1 mm central macular thickness was measured with optical coherence tomography (OCT) (Stratus III, Carl Zeiss Meditec, Dublin, CA, USA). The time of onset of macular edema or ocular complications and the follow-up period were recorded. The numbers of intravitreal injections of bevacizumab were recorded. Fluorescein angiography was performed on all patients to record the UME before and after treatment. All topical and systemic medications such as methotrexate, cyclosporine, azathioprine, steroids, infliximab, and antituberculosis therapy were continued during the follow-up period as required.

The diagnosis of presumed ocular tuberculosis was made based on clinical findings of chorioretinitis, granulomatous uveitis, positive PPD of 15 mm of induration or greater, positive response to antituberculosis therapy within 4 weeks, and exclusion of other causes of uveitis as previously reported [35]. Minimum followup was three months. The institutional review boards of both study centers approved this study.

2.1. Intravitreal Bevacizumab. After discussing the details of the intravitreal injection with each patient, all patients read and signed an informed consent prior to the procedure. The pupil was dilated, and topical anesthesia and topical moxifloxacin 0.5% were instilled. The lids and lashes were cleansed with povidone iodine 10% solution and a sterile drape was placed over the eye. A sterile lid speculum was inserted. Povidone iodine 5% ophthalmic solution was instilled and, after 90 seconds, rinsed with saline solution. A swab soaked in 5% povidone iodine was placed on the conjunctiva at the site of injection. A 0.05 mL solution containing 1.25 mg of bevacizumab was injected intravitreally. The bevacizumab was prepared in the compounding pharmacy. The injection site was 3.5 mm posterior to the limbus for phakic patients and 3 mm for pseudophakic and aphakic patients and injection was performed with a 30-gauge needle avoiding the horizontal meridians and aiming at the center of the globe. Broad spectrum antimicrobial eye drops were instilled at the end of the procedure and patients were instructed to continue topical antimicrobial drops four times daily for one week. Patients were requested to return at weekly intervals.

2.2. Control of Inflammation and Repeated Intravitreal Injections. Intraocular inflammation was graded during each follow-up visit based on the recommendations of the Standardization of Uveitis Nomenclature (SUN) working group [36]. The number of intravitreal injections of bevacizumab was correlated with the activity of the disease. Retreatments of intravitreal bevacizumab (up to one injection per month) were performed as required during the three-month follow-up period. The pre- and postinjection visual acuity was converted from Snellen to LogMAR scale.

2.3. Statistical Analyses. Descriptive statistics such as means, standard deviation, and percentages were calculated. Statistical analyses were performed to determine the mean change from baseline visual acuity to 1 month and 3 months of followup. The mean change from baseline retinal thickness using OCT was analyzed at 1 and 3 months. Statistical analyses were performed using repeated measure analyses of variance (ANOVA). All P values were two-sided and the significance level was set at 0.05. Data analyses were performed with SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The cohort comprised 41 patients of which 21 were female and 20 male. The mean age of patients was 41 ± 16 years with a mean followup of 4 ± 1 months. Patients were divided into four groups: idiopathic intermediate uveitis (10 patients) (Figure 1); Behcet's disease (9 patients); idiopathic panuveitis (10 patients); and presumed ocular tuberculosis uveitis group (12 patients) (Figure 2).

The mean LogMAR visual acuity for the study cohort improved from a baseline value of 0.8 ± 0.8 to 0.4 ± 0.5 at 1 month and 0.3 ± 0.5 at 3 months. The improvement in visual acuity at 3 months was statistically significant ($P < 0.002$) (Table 1). There was a continuous increase in mean

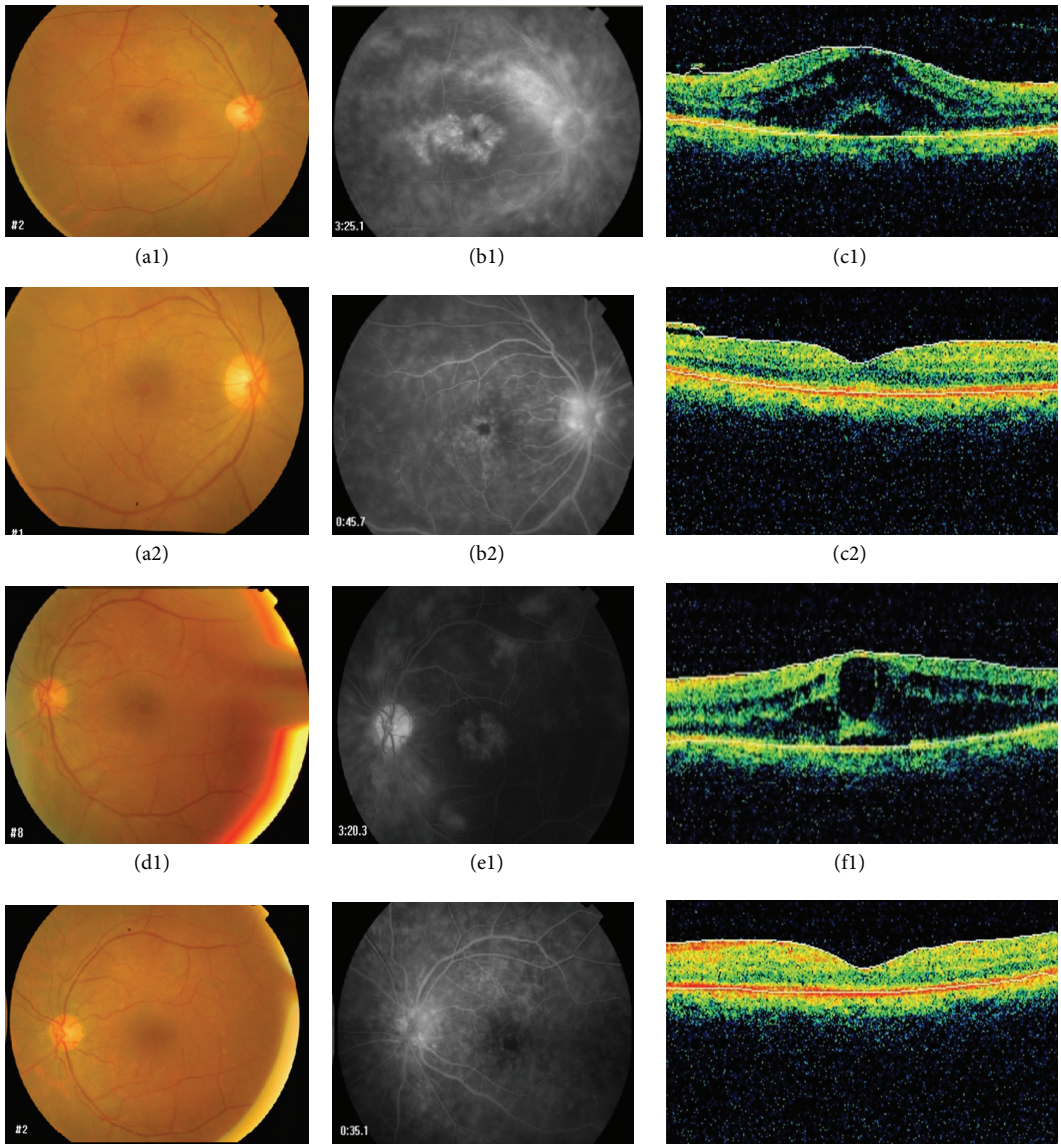

Figure 1: A 56-year-old female with bilateral idiopathic intermediate uveitis and chronic cystoid macular edema. (a1), (b1), and (c1) and (d1), (e1), and (f1) are the fundus photos, fluorescein angiograms, and optical coherence tomography prior to treatment with intravitreal bevacizumab in both eyes. (a2), (b2), and (c2) and (d2), (e2), and (f2) are the fundus photos, fluorescein angiograms and optical coherence tomography, after treatment with intravitreal bevacizumab, which show the response of CME after intravitreal bevacizumab.

visual acuity over the duration of followup in each group (Table 1). The baseline macular thickness for the study cohort was 430 ± 132 μm. Following intravitreal bevacizumab, the macular thickness improved to 286 ± 93 μm at 1 month and to 265 ± 88 μm at 3 months. The improvement in macular thickness at 3 months was statistically significant ($P < 0.001$) (Table 1).

The change in visual acuity and macular thickness for each group is presented in Table 1. All groups had an increase in mean visual acuity after intravitreal bevacizumab (Table 1). The greatest reduction in macular thickness occurred at 1 month in Behcet's disease group, but the edema reappeared by 3 months (Table 1). All other groups had a continuous reduction in macular thickness at 3 months (Table 1). The greatest reduction in macular thickness from baseline to 3 months occurred in the idiopathic intermediate uveitis group (Table 1).

Thirteen (32%) out of 41 patients received more than one intravitreal bevacizumab injection. Eight of these patients had uncontrolled intraocular inflammation and 5 (15%) of 33 patients ($P < 0.001$) had well-controlled intraocular inflammation.

No systemic or ocular complications were noted following intravitreal bevacizumab. A transient rise in intraocular pressure following intravitreal bevacizumab was observed in 14 (34%) patients.

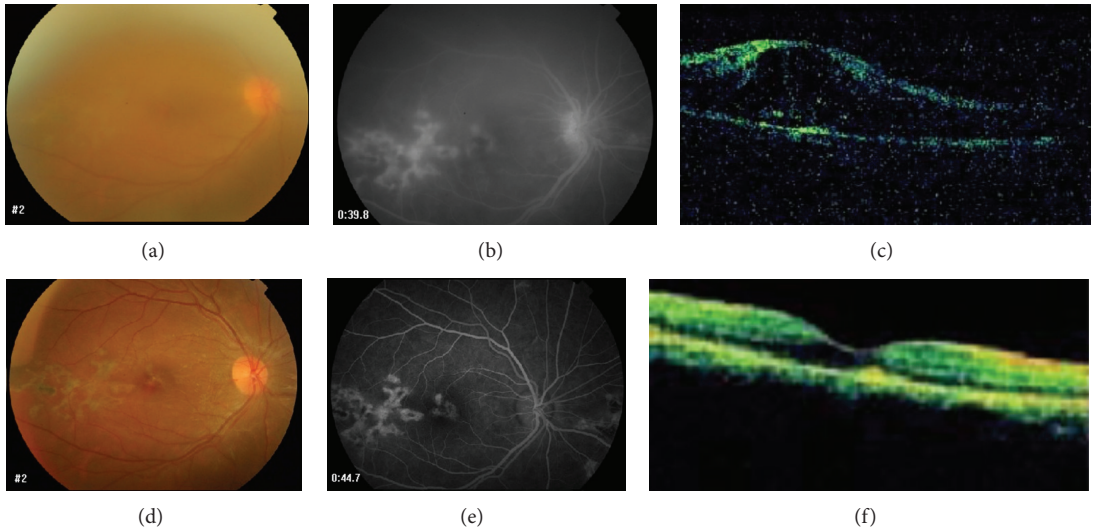

Figure 2: A 28-year-old female with presumed intraocular tuberculosis, choroiditis, and cystoid macular edema in the right eye. (a), (b), and (c) are the fundus photos, fluorescein angiograms, and optical coherence tomographies, prior to treatment with intravitreal bevacizumab. (d), (e), and (f) are the fundus photos, fluorescein angiograms, and optical coherence tomography, after treatment with intravitreal bevacizumab, which shows good response.

Table 1: Demographics, visual acuity, and macular thickness of patients with uveitic cystoid macular edema treated with intravitreal bevacizumab.

	IIU	BD	IPU	POTBU	*P* value
Number of patients	10	9	10	12	
Mean age	44 ± 16	34 ± 7	28 ± 13	43 ± 17	
Mean followup	4 ± 1	4 ± 1	4 ± 1	3.9 ± 2	
Mean number of Avastin injections	1.2 ± 0.4	1.7 ± 0.7	1.6 ± 0.7	1.6 ± 0.5	
Mean initial VA	0.5 ± 0.8	0.8 ± 0.8	0.8 ± 0.8	0.8 ± 0.5	
Mean 1-month VA	0.3 ± 0.4	0.4 ± 0.8	0.5 ± 0.8	0.5 ± 0.8	
Mean 3-month VA	0.2 ± 0.4	0.2 ± 0.5	0.3 ± 0.5	0.4 ± 0.5	<0.002
Mean initial OCT thickness (μm)	437 ± 121	433 ± 179	342 ± 83	404 ± 134	
Mean OCT thickness (1 month) (μm)	314 ± 120	259 ± 102	270 ± 45	296 ± 94	
Mean OCT thickness (3 months) (μm)	246 ± 80	284 ± 106	239 ± 49	281 ± 110	<0.001

P value (ANOVA) was assessed for the mean OCT retinal thickness and the mean LogMAR change in visual acuity form baseline.
IIU: idiopathic intermediate uveitis, BD: Behcet's disease, IPU: idiopathic panuveitis, POTBU: presumed ocular tuberculosis uveitis, VA: visual acuity, and OCT: optical coherence tomography.

4. Discussion

Uveitis is an important cause of ocular morbidity, as it can cause progressive, relentless destruction of visually important structures such as the macula. Immune-mediated inflammation of the uvea afflicts 1.15 per 1,000 individuals in the western hemisphere [37]. Chronic UME is frequently seen in patients with chronic uveitis. The therapeutic strategy for immune-mediated uveitis is evolving as new therapeutic modalities emerge. Immune-mediated insults initiate a chain of events at the cellular and molecular levels leading to an upregulation of several cytokines such as VEGF which is upregulated in patients with uveitis [5–8, 10].

Currently, there is no standard treatment for managing UME associated with chronic uveitis. Currently available treatment consists of topical nonsteroidal anti-inflammatory, oral, periocular, and intraocular injections of corticosteroids, as well as oral carbonic anhydrase inhibitors, systemic somatostatin analogs, and recently interferon alpha, mycophenolate mofetil, and VEGF inhibitors [11–20].

The outcomes of the current study indicate that intravitreal bevacizumab is effective, tolerable, and safe for the management of UME associated with uveitis. For example, there was a significant reduction in UME indicated by the decrease in macular thickness. Additionally, there was a concomitant improvement in visual acuity in patients suffering from idiopathic intermediate uveitis, panuveitis, Behcet's disease, and presumed ocular tuberculosis. These outcomes indicate that anti-VEGF treatment, which has no immunosuppressive effects may serve as a safe treatment for UME in patients with infectious uveitis. Our results concur with several reports that have described an improvement in macular edema and

regression of ocular neovascularization following intravitreal bevacizumab for uveitis [7, 10, 29–31, 33]. The improvement of macular edema after intravitreal bevacizumab was transient and short-lived in several studies [30, 31, 38]. In this study, we found that adequate control of intraocular inflammation is associated with reduction in the number of intravitreal bevacizumab reinjection. Uncontrolled intraocular inflammation may lead to recurrence of UME which would warrant repeat injections of bevacizumab. We found that intravitreal bevacizumab with the control of inflammation affords long-term remission of UME. For example, only 5 out of 33 patients with controlled intraocular inflammation required more than one injection of intravitreal bevacizumab in comparison to 8 patients with uncontrolled active intraocular inflammation who received more than one injection ($P < 0.001$). Repeat injections were indicated in patients with active uveitis. We believe that bevacizumab is an important adjuvant treatment to appropriate therapies for the management of UME associated with infectious or noninfectious uveitis due to the lack of an immunosuppressive effect and the safety and efficacy.

Some limitations of this study include the retrospective review and short follow-up period. However, consecutive patients irrespective of outcome were selected over the time period of this study to mitigate some of the drawbacks.

In conclusion, cases with well-controlled intraocular inflammation that receive adjunct intravitreal bevacizumab result in long-term remission of UME. In cases of UME associated with infectious uveitis, the lack of immunosuppression from intravitreal bevacizumab treatment will not interfere with the immune response. Longer-term prospective studies are required to confirm the observation in this study.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Review Article

Examining the Choroid in Ocular Inflammation: A Focus on Enhanced Depth Imaging

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The choroid is the vascular layer that supplies the outer retina and is involved in the pathogenesis of several ocular conditions including choroidal tumors, age related macular degeneration, central serous chorioretinopathy, diabetic retinopathy, and uveitis. Nevertheless, difficulties in the visualization of the choroid have limited our understanding of its exact role in ocular pathology. Enhanced depth imaging optical coherent topography (EDI-OCT) is a novel, noninvasive technique that is used to evaluate choroidal thickness and morphology in these diseases. The technique provides detailed objective *in vivo* visualization of the choroid and can be used to characterize posterior segment inflammatory disorders, monitor disease activity, and evaluate efficacy of treatment. In this review we summarize the current application of this technique in ocular inflammatory disorders and highlight its utility as an additional tool in monitoring choroidal involvement in ocular inflammation.

1. Introduction

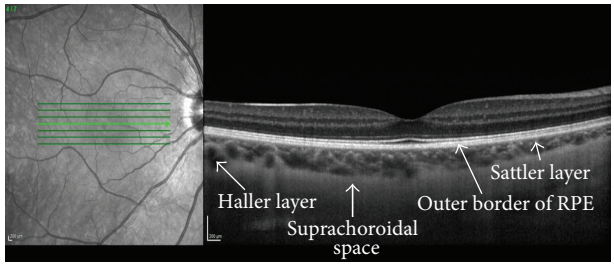
The choroid is the posterior portion of the uveal tract and outlines the retina and retinal pigment epithelium (RPE) [1]. It comprises three vasculature layers: Haller layer that includes large vessels, Sattler layer with medium vessels occupying choroidal stroma (Figure 1), and the innermost layer of choriocapillaris that is in contact with Bruch's membrane [1]. It provides up to 85% of the ocular blood flow and is solely responsible for the blood supply to the outer two thirds of the retina [1, 2].

The choroid has been implicated in the pathogenesis of many posterior segment inflammatory disorders, including Vogt-Koyanagi-Harada syndrome (VKH) [3], Behçet's disease [4, 5], sarcoidosis [6, 7], birdshot chorioretinopathy [8, 9], sympathetic ophthalmia [10, 11], panuveitis [12], toxoplasmosis [13], and posterior scleritis [14]. Due to the location of the choroid under the RPE most clinically available imaging modalities including fundus fluorescein angiogram (FFA), B-Scan ultrasonography, and optical coherence tomography (OCT) provide only partial information regarding its structure and function. This is mainly due to signal loss and light scattering at the RPE layer that is highly reflective and blocks most signals from the choroid [15].

Indocyanine green angiography (ICGA) is a technique that uses tricarbocyanine dye to visualize the choroid and delineate the choroidal circulation [16, 17]. Despite its role in evaluating inflammatory lesions in several conditions [8, 17, 18], its use is limited due to the fact that it is an invasive procedure [17]. Unlike OCT, ICGA lacks depth information and does not provide cross-sectional images of the choroid. These problems limit its role in patients' follow-up [19].

2. Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT)

OCT uses the principle of low coherence interferometry to obtain in-depth information from various retinal structures to create cross-sectional images. It is an extremely useful tool for visualizing and defining different retinal layers and it helps identify retinal pathology. However, OCT is limited to imaging the retina and optic nerve head and generally cannot penetrate the RPE. Recent developments have improved



(a) (b)

Figure 1: Enhanced depth optical coherence tomographic B-scan using a Heidelberg Spectralis OCT (Heidelberg Engineering, Germany). (a) Near-infrared fundus image, (b) corresponding EDI-OCT demonstrating normal retinal and choroidal anatomy at the macula. Note that both retinal and choroidal layers can be clearly identified on the same scan.

its capability in imaging deeper structures, including the choroid. This technique, term enhanced depth imaging (EDI) (Figure 1), provides detailed information of the choroid by displacing the zero delay point, which is the point of maximal OCT signal sensitivity. Placing the zero delay point closer to the choroid rather than the inner retinal layers results in an enhanced visualization of the choroid and enables quantitative measurement of its thickness with high reliability and reproducibility [15, 20, 21].

3. Choroidal Thickness

Choroidal thickness is measured by calculating the distance from the hyperreflective line representing the outer border of the RPE (Figure 1) to the inner edge of the suprachoroidal space, which is represented by a hyporeflective line on the EDI-OCT (Figure 1). Although choroidal thickness is routinely measured manually using the digital caliper of the machine [15, 22] or by a validated custom image grading software [23, 24], automated software is available [25]. Using EDI, the mean subfoveal choroidal thickness in normal individuals has been estimated to be between 287 μm and 335 μm [15, 26, 27]. The variation in choroidal thickness is probably due to several variables such as gender, where choroidal thickness in men was found to be 62 μm greater than in women [28]; age, with progressive subfoveal choroidal thinning at a rate of 15.6 μm per decade [26, 29]; axial length and the refractive state of the eye also affecting choroidal thickness with each diopter of myopia resulting in a 8.7 μm reduction in choroidal thickness [30]. Topographic variation in choroidal thickness also occurs with the maximal thickness at the subfoveal area and the thinnest nasally and inferiorly [23, 26].

The EDI-OCT technique has been used to evaluate the choroid in cases of choroidal tumors [31], diabetic macular oedema [32], glaucoma [33], age related macular degeneration [34], central serous chorioretinopathy [35], and age related choroidal atrophy [29]. In this paper we look at the application of EDI-OCT in ocular inflammatory disorders and highlight its potential in monitoring choroidal changes, which may provide an additional tool for better management in these disorders.

4. EDI-OCT Scan in Ocular Inflammatory Disorders

4.1. EDI-OCT in Noninfectious Uveitis

4.1.1. Vogt-Koyanagi-Harada Disease. Vogt-Koyanagi-Harada disease (VKH) is a multisystemic, granulomatous inflammatory disorder with presumed T-cell mediated autoimmune dysregulation towards melanocytes. The disease has four clinical phases, prodromal, acute, chronic (convalescent), and chronic recurrent, and is characterized by ocular, dermatological, and neurological involvement [3]. In the eye it is characterized by bilateral granulomatous panuveitis that initially presents as diffuse choroiditis with multifocal serous detachments that may coalesce into an exudative retinal detachment. Later during the course of the disease, signs of chorioretinal depigmentation, sunset glow fundus, or perilimbal vitiligo (Sugiura sign) are seen. Patients may also develop recurrent or chronic anterior uveitis during the chronic stage of the disease [36].

In a study of EDI-OCT scans during the acute stage of VKH a marked increase in the average subfoveal choroidal thickness was found in sixteen eyes of eight patients (805 ± 173 μm). Following systemic steroid therapy and resolution of the inflammation, this declined by day fourteen to 341 ± 70 μm [37]. An EDI-OCT of a representative case from this cohort is illustrated in Figure 2 demonstrating an enlargement of the subfoveal choroidal thickness during acute VKH with subsequent resolution with treatment.

In a second study of five eyes of patients with new onset VKH, following reduction of choroidal thickness with treatment, EDI-OCT was useful in detecting rebound choroidal thickness described as an increase of more than 100 μm in the absence of other clinical signs of inflammation [38]. Morphological changes in the choroid of VKH patients were also described by another group who looked at twelve eyes of six patients with acute and chronic VKH. The authors reported a significant increase in choroidal thickness of 424 ± 50.1 μm during the acute stage of the disease and a loss of the hyperreflective dots in the inner choroid during both acute and chronic phases, which may reflect changes in choroidal vasculature that occur with inflammation [39]. The role of EDI-OCT in detecting subclinical recurrence after resolution of the acute inflammation was demonstrated in a 71-year-old patient who presented six months after his initial diagnosis of VKH with headache, tinnitus, bilateral sensorineural hearing loss, and rebound choroidal thickening in the absence of other signs of ocular inflammation. The patient was taking 5 mg oral prednisolone on alternate days at presentation and increasing the dose to a 100 mg per day led to a speedy resolution of the hearing loss and a reduction in the choroidal thickness [40].

Ocular depigmentation that appears as sunset glow fundus is a predominant feature in the chronic stage of VKH [36]. In a study that looked at 19 patients with chronic

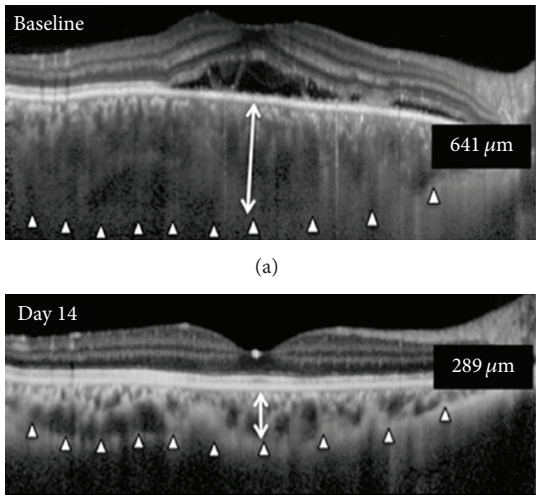


Figure 2: Enhanced depth optical coherence tomographic B-scan of the right eye of a 35-year-old patient with VKH taken using Heidelberg Spectralis OCT (Heidelberg Engineering, Germany). Arrowheads delineate the outer border of the choroid. At baseline subfoveal choroidal thickness of 641 μm with serous retinal detachment, this was reduced with steroid therapy by day 14 to 289 μm with resolution of serous retinal detachment. (Reprinted with permission from "Subfoveal choroidal thickness after treatment of Vogt-Koyanagi-Harada disease" [37].)

VKH who were in remission with no immunosuppressive treatment for over 3 years, the subfoveal choroidal thickness was found to be significantly and inversely correlated with the amount of fundus pigmentation, the area of peripapillary atrophy, and the duration of the disease. The mean subfoveal choroidal thickness was 144 ± 72 μm in patients with severe depigmentation of the fundus, 249 ± 35 μm in patients with no or mild depigmentation of the fundus, and 227 ± 58 μm in the controls [41]. A similar finding of progressive choroidal thinning in chronic VKH was also observed by another group, in a cohort of 16 patients with VKH [42]. EDI-OCT demonstrates that in VKH the choroid seems to thicken at times of active acute inflammation and reduces in thickness during the chronic phase. It provides a noninvasive tool to monitor disease activity and help treatment decisions.

4.1.2. Behçet's Disease. Behçet's disease (BD) is an idiopathic multisystemic disease that affects many organs and is characterized by oral, genital mucocutaneous ulceration, skin lesions, and uveitis. The disease is most prevalent in the Mediterranean region as well as Japan and is associated with the HLA-B5 allele. Ocular BD is frequently bilateral and mainly presents with acute bilateral nongranulomatous panuveitis, occlusive diffuse vasculitis, retinitis, and vitritis [43].

Two studies have evaluated choroidal thickness in BD using EDI-OCT scans. The first one looked at 30 eyes from 30 Korean patients and compared the subfoveal choroidal thickness in these eyes during the active and quiescent phases of posterior uveitis. Subfoveal choroidal thickness during the acute stage (398.77 ± 155.59 μm) was significantly greater than the quiescent phase of the disease (356.72 ± 141.09 μm) and significantly correlated with the amount of leakage on the FFA [22]. This was attributed to choroidal infiltration by inflammatory cells and matched earlier immunohistopathological studies [4]. Interestingly, during the quiescent phase of the disease, defined as no clinical signs of inflammation in the eye for at least three months with resolution of vascular leakage on the angiogram, subfoveal thickness was still significantly greater than in healthy controls (259.96 ± 65.16 μm). This possibly reflects persistent subclinical inflammation, and further investigations such as FFA and ICGA may be needed. Also of interest was a lack of significant difference in choroidal thickness between the two eyes in patients with unilateral BD, raising the possibility of choroidal infiltration of the fellow, clinically uninvolved eye during disease exacerbations. No significant correlation between choroidal thickness and the duration of the disease was observed in this study [22].

A second study that was conducted in Turkey compared the subfoveal choroidal thickness between BD patients without ocular involvement and those with BD uveitis during the active and quiescent phases of inflammation. The study looked at the subfoveal choroidal thickness in 35 eyes from 35 patients with BD posterior uveitis (289 ± 74 μm), 35 eyes from 35 BD with no ocular involvement (337 ± 88 μm), and 30 eyes of healthy individuals that were used as controls (329 ± 64 μm). This relative thinning in eyes of BD posterior uveitis patients may be attributed to progressive fibrosis and thinning of the choroid that usually happens during the first 2-3 years of the BD, possibly due to choroidal ischemic changes from the recurrent inflammation [44]. These findings might be due to different cohorts at various stages of the disease and perhaps suggest the need for future studies to further explore choroidal activity during BD.

4.1.3. Sarcoidosis. Sarcoidosis is a T-cell mediated, multisystemic, granulomatous inflammatory disorder of unknown etiology. The ocular presentation of sarcoidosis is variable and manifests as anterior, intermediate, or panuveitis. Multifocal choroiditis, choroidal and optic disc granulomas, and segmental and rarely occlusive phlebitis may also be seen [45, 46].

There is only one case report on the morphological characterization of a choroidal sarcoid granuloma using EDI-OCT in a 63-year-old patient with biopsy proven systemic sarcoidosis. The choroidal granulomas were seen as homogenous, hyporeflective demarcated lesions that reduced in size with commencement of immunosuppressant treatment [47]. Healthy choroidal tissues between these lesions and subretinal fluid adjacent to the peripapillary choroidal lesions were demonstrated [47]. This indicates the prospective of EDI-OCT in evaluating morphological changes of the choroid in ocular sarcoidosis and demonstrating response to treatment.

4.1.4. Birdshot Chorioretinopathy. Birdshot chorioretinopathy (BSCR) is an idiopathic bilateral chorioretinopathy, characterized by deep oval, creamy white indistinct choroidal

lesions. These lesions radiate from the disc towards the equator and are frequently associated with mild vitritis. The majority of affected patients have a positive HLA-A29 allele and FFA usually shows venous hyperfluorescence with extensive late intraretinal and disc leakage [9].

In a study of twenty four eyes of twelve patients with clinically active or quiescent BSCR, both macular and extramacular EDI-OCT scans were taken and compared to healthy controls [23]. BSCR patients were found to have a generalized retinal thinning with loss of the photoreceptor inner-outer segment junction, significant subfoveal choroidal thinning ($276 \pm 101\,\mu$m) in comparison with controls ($337 \pm 74\,\mu$m), absence or thinning of the Sattler vessel layer, and extramacular choroidal thinning [23], which could be attributed to late stage of BSCR. The clinically observed chorioretinal lesions corresponded to hyporeflective spots due to choroidal depigmentation and were surrounded by choroidal vessels on the EDI-OCT scan. Some patients also displayed discrete hyperreflective spots surrounding the BSCR lesions, thought to represent either pigmentary or inflammatory cellular infiltrate [23]. On ICG, BSCR lesions were identified as dark hypofluorescent spots with a tendency of active lesions to become isofluorescent during the late phase of the ICG [8]. This suggests EDI-OCT may be used as a noninvasive tool to monitor choroidal involvement in BSCR.

4.1.5. Sympathetic Ophthalmia (SO). Sympathetic ophthalmia is a granulomatous panuveitis typically occurring after penetrating trauma or surgery to one eye (the exciting eye), that eventually threatens the vision in the contralateral eye (the sympathizing eye) [10].

In a 39-year-old male, who had a penetrating injury to his left eye associated with uveal tissue prolapse, an EDI-OCT scan was useful in delineating the choroidal inflammation and the response to therapy. This patient presented one month after his initial trauma with blurred vision in the right eye [48]. Wide-field FFA showed multiple pinpoint areas of leakage at the right posterior pole, and an EDI-OCT scan revealed subfoveal fluid and a choroidal thickness of more than $500\,\mu$m in that eye. Following treatment with prednisolone at 60 mg per day a reduction of choroidal thickness in the right eye to $237\,\mu$m was noted. The diagnosis of SO was confirmed by histopathological examination of the left eye after elective enucleation. In this case, reduction in choroidal thickness on EDI-OCT was valuable in monitoring the response to treatment, which was in keeping with an improvement in vision [48].

4.1.6. Idiopathic Panuveitis. Panuveitis is an intraocular inflammation that affects the anterior chamber, vitreous, retina, and/or choroid [49]. Panuveitis can be associated with several diseases; however, a relatively large number of cases remain idiopathic [12]. In a study that compared 21 eyes of 21 patients with inactive idiopathic panuveitis to healthy controls, the severity of the disease was correlated with the degree of choroidal thinning where patients had average choroidal thickness of $233.7 \pm 73.3\,\mu$m, which was thinner than controls. This was attributed to thinning of Haller's vessel layer and hyporeflectivity that is possibly due to loss of luminal spaces in choroidal vasculature, which might implicate Haller's layer in the pathophysiology of idiopathic panuveitis [24]. EDI-OCT may provide an accurate way to further understand the role of choroid in idiopathic panuveitis.

4.2. EDI-OCT in Infectious Uveitis

4.2.1. Toxoplasma Retinochoroiditis. *Toxoplasma gondii* is the commonest cause of posterior uveitis in immunocompetent patients [50]. Reactivation of toxoplasmosis is characterized by focal retinitis adjacent to an old scar and is usually associated with vitritis that can be severe [51].

Choroidal changes in patients with toxoplasma retinochoroiditis were evaluated in 19 eyes of 15 patients with primary or reactivated toxoplasmosis. During the active stage there was a marked increase in choroidal thickness under the active lesion, demonstrated by increased hyporeflectivity on EDI-OCT. This was thought to be secondary to thickening of the retinal layers. The mean choroidal thickness declined from $390 \pm 245\,\mu$m during the active stage of the disease to $189 \pm 86\,\mu$m at last follow-up. No change in subfoveal choroidal thickness was observed during any phases of disease [52]. During the inactive phase of toxoplasmosis, four types of retinochoroidal scars were identified, atrophic scars that were associated with choroidal thinning, elevated retinochoroidal scaring associated with normal choroidal thickness, combined scars (atrophic + elevated) with mixed features of both, and deep scars that were associated with significant thinning of the choroid with loss of normal choroidal architecture [52]. These findings suggest the potential of EDI-OCT in morphological characterization of the choroidal and retinal changes in ocular toxoplasmosis.

4.2.2. Fungal Choroidal Granuloma. Endogenous fungal endophthalmitis is a devastating intraocular infection that haematogenously spreads to the eye from a distant source of infection [53]. Painful reduction of vision and photophobia are the usual presenting symptoms due to either anterior or posterior segment inflammation. It is a potentially blinding condition and the rate of visual loss was found to be higher with *Candida* species [54]. There are several predisposing factors for developing fungus endophthalmitis including systemic diseases such as diabetes mellitus malignancies, organ failures, and transplantation. Recent hospitalization with long-term indwelling lines, immunosuppressive therapy, intravenous drug abuse, and intraocular surgeries are also related to an increased risk [53]. Nevertheless, the disease has also been reported in immunocompetent patients [55, 56]. In a 58-year-old immunocompetent patient, who presented with sudden painful uniocular blurred vision and panuveitis with a patch of chorioretinitis, a well demarcated choroidal mass was detected on EDI-OCT scans. A positive aqueous tap for panfungal genome confirmed the diagnosis of fungal choroidal granuloma and the choroidal lesion responded and reduced in size following successful antifungal treatment with fluconazole [56]. This case suggests the benefit of EDI-OCT scans in assessing such patients and confirming response to treatment [56].

4.3. EDI-OCT in Posterior Scleritis. Scleritis is a serious, painful, and potentially blinding inflammation that affects the sclera. The disease can involve the anterior or the posterior sclera and may have local or systemic associations. Posterior scleritis may present with serous retinal detachments, optic disc swelling, or choroidal effusions [57].

The choroid, being in a close apposition to the sclera, is found to be thickened during acute attacks and thinned after repeated episodes of posterior scleritis. In two cases with new onset acute noninfectious posterior scleritis a marked thickening of the choroid was noted [58]. In a 58-year-old patient who presented with unilateral pain and serous retinal detachment, the subfoveal choroidal thickness in the affected eye was found to be 548 μm. Following systemic steroid treatment, choroidal thickness reduced to 308 μm at two weeks and to 226 μm at six months. In a second case, a 65-year-old patient presented with bilateral ocular redness and pain. The subfoveal choroidal thickness was 447 μm in the right eye and 446 μm in the left eye, and after treatment with systemic steroids it reduced to 393 μm in the right eye and 375 μm in the left eye at two weeks. By two months the sclera reduced in thickness to 372 μm in the right eye and 374 μm in the left eye [58]. Interestingly, in two other cases of young patients with unilateral acute recurrent posterior scleritis the choroid was significantly thinner than the unaffected eye [59]. Recurrent inflammatory changes in the sclera are thought to induce atrophic changes in the choroid resulting in progressive choroidal thinning. In a 33-year-old-patient with recurrent unilateral posterior scleritis, who was symptom-free for over two years on a maintenance dose of immunosuppression, following a relapse he presented with ocular pain and serous retinal detachment with a subfoveal choroidal thickness of 220 μm. The subfoveal choroidal thickness in the contralateral uninvolved eye was 375 μm. Increasing the immunosuppression was associated with resolution of symptoms and reduction of choroidal thickness in the involved eye to 143 μm while the choroidal thickness in the contralateral eye measured 390 μm at 35-month follow-up. A similar finding was observed in a second young patient who relapsed 53 months after his initial presentation with a unilateral serous retinal detachment and presented with a subfoveal choroidal thickness of 235 μm in the affected eye and 374 μm in the uninvolved contralateral eye. This reduced with restarting prednisolone treatment to 198 μm while the other eye maintained the same subfoveal choroidal thickness of 374 μm at 59-month follow-up. These findings suggest the possibility of monitoring severity of inflammation and the response to treatment during acute attacks of posterior scleritis as well as during relapses.

5. Conclusion

EDI-OCT is a noninvasive reproducible technique that allows enhanced visualization and *in vivo* measurement of choroidal thickness that could be superior to B-scan ultrasound, which has low resolution and can be less reliable when used by inexperienced examiners. Though it may be difficult to delineate the inner edge of the suprachoroidal space, especially during acute inflammation, choroidal thickness remains a promising parameter that can be used to characterize different disease entities and monitor resolution of posterior pole inflammatory disorders and efficacy of treatment. The exact behavior of the choroid in these conditions remains unclear and further prospective studies are required to help us clarify its role in the pathogenesis of these disorders.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Management of Uveitis-Related Choroidal Neovascularization: From the Pathogenesis to the Therapy

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Inflammatory choroidal neovascularization is a severe but uncommon complication of uveitis, more frequent in posterior uveitis such as punctate inner choroidopathy, multifocal choroiditis, serpiginous choroiditis, and Vogt-Koyanagi-Harada syndrome. Its pathogenesis is supposed to be similar to the wet age related macular degeneration: hypoxia, release of vascular endothelial growth factor, stromal cell derived factor 1-alpha, and other mediators seem to be involved in the uveitis-related choroidal neovascularization. A review on the factors implicated so far in the pathogenesis of inflammatory choroidal neovascularization was performed. Also we reported the success rate of single studies concerning the therapies of choroidal neovascularization secondary to uveitis during the last decade: photodynamic therapy, intravitreal bevacizumab, and intravitreal ranibizumab, besides steroidal and immunosuppressive therapy. Hereby a standardization of the therapeutic approach is proposed.

1. Introduction

Beside the well-known choroidal neovascularization (CNV) in the age related macular degeneration (ARMD) in myopic eyes or in angioid streaks, neovascular membranes can develop even as a complication of uveitis with an incidence of 2% [1], accounting for severe visual loss in patients with ocular infectious or noninfectious inflammatory diseases [2], also affecting young patients.

The prevalence of CNV secondary to uveitis varies among different entities, commonly occurring in presumed ocular histoplasmosis (POHS) (3.8%), toxoplasmosis, punctate inner choroidopathy (PIC) (17–40%), idiopathic multifocal choroiditis (MC) (33%), and serpiginous choroiditis (SC) [2]. Yet, CNV has been reported in up to 9% of patients with Vogt-Koyanagi-Harada disease (VKH) [1, 3].

2. Diagnosis

Inflammatory CNV can develop close to chorioretinal scar or choroidal granuloma and is classified topographically as foveal, juxtafoveal, or extrafoveal. The first is often early recognized by the patient himself complaining of metamorphopsia or central scotoma and can lead to the diagnosis of a subclinical posterior or intermediate uveitis. Otherwise, an extrafoveal membrane may be asymptomatic and can be found only at a follow-up examination or in case of posterior pole acute hemorrhage. As in ARMD, the microscopical features define type 1 or type 2 membrane, if it invades or not the subretinal space. In uveitis the classic membrane strongly shows the main type; it has a grayish appearance with an evidence of exudative or hemorrhagic foci surrounding the lesion. However, opthalmoscopically subretinal membrane could be missed because of very few levels of exudation; the only indirect sign could be a small intraretinal hemorrhagic lesion. Atrophic CNVs are yellow-white plaques. Often a bigger CNV can have a mixed pattern, bearing active foci in a globally fibrous plaque. A membrane can manifest only with macular edema or serous retinal detachment; however, macular edema and serous retinal detachment also can represent signs of inflammation found in course of intermediate/posterior uveitis, leading sometimes to a misdiagnosis or imprecise evaluation of the activity of the underlying disease.

In this case the role of the diagnostic imaging is crucial. Fluorescein angiography (FA) has been for long time the

principal way to assess the presence and the activity of a CNV in uveitic patients, showing early hyperfluorescence in the choroidal phase and late leakage, associated sometimes with screen effect in presence of blood or pigment. Indocyanine green angiography (ICG) is useful for highlighting the feeder vessel or occult membranes; the new Heidelberg SLO video ICG enhances the diagnostic potentialities of this procedure. Nowadays a growing role is played by optical coherence tomography (OCT), a fast, noninvasive instrument able to assess the presence and the activity of the disease. Kotsolis et al. [4] showed that FA has a greater capability to detect the membrane features compared to OCT. But in the study of Kotsolis et al. [4] time domain OCT was used mostly; theoretically using the spectral domain OCT this discrepancy is unlikely to be observed, even though a definitive study still lacks.

3. Pathogenesis

Given the low incidence of inflammatory CNV and the difficulty in obtaining a reliable experimental model, most of our knowledge about this disease is mutated from the histopathological studies on ARMD-related CNV, supposing that similar clinical features correspond to common biological pathways.

In CNV a key role of vascular endothelial growth factor (VEGF) in the new blood vessels development has been widely demonstrated [5, 6].

VEGF is produced by endothelial cells, pericytes, Müller cells, Ganglion cells, photoreceptors, and RPE cells that can produce the growth factor in a polarized way towards Brüch's membrane and choriocapillaris [7, 8]. The major signal to the production of these cytokines seems to be the hypoxia via the activation of hypoxia induced factor (HIF) pathways [9]. Four major VEGF isoforms exist: 2 diffusive forms for intercellular signaling (VEGF-121 and VEGF-165) and 2 heparin binding heavier forms (VEGF-189 and VEGF-206) [10]. The cytokines promote secretion of matrix metalloproteinases that cut and activate [11] the VEGF-165 and possibly degrade the extracellular meshwork allowing heavier form to be released and then activated after a plasmin dependent cleavage.

The endothelial progenitor cells (EPCs) are attracted by the stromal cell derived factor 1-alpha (SDF1) that is known to be secreted by hypoxic or damaged retinal pigment epithelium (RPE) or retina [12, 13]. The only known receptor for SDF1 is CXCR4 that is expressed on the EPC and is responsible for their chemotaxis toward the damaged tissue. CXCR4 can also be expressed by some leukocytes that are involved in the membrane formation.

Guerin et al. [14] performed a detailed study on CNV of various etiologies, testing some of the most known hypothesis on this subject. There were some unavoidable biases in the study: for example, only advanced and partially fibrous membranes were collected, often unresponsive to the previous therapy. They suggest that RPE cells may play an important role in the development of CNV, the SDF1/CXCR4 axis is present in human, and there is a statistically significant association between detectable SDF1 and the neovascularization marker VEGFR-2.

Furthermore we performed an adjunctive statistical analysis on the dataset reported by Guerin: using Mann-Whitney test (in R environment [15]) we tested if immunohistochemical staining grading of the three main tissues (RPE, vascular network, and fibroblasts) for SDF1, CXCR4, and VEGFR-2 differs between inflammatory CNV and ARMD. In Table 1 the P values of the comparisons are reported. The study is underpowered for most of the comparisons but, interestingly, a low P value was found for the CXCR4 staining of the vascular meshwork of uveitis-related CNV versus ARMD-related CNV, suggesting that capillaries have a different role in the membrane development. Further studies on this distinctive aspect should be necessary.

CNV has also an extravascular component consisting in fibroblasts and leucocytes that express the CXCR4 themselves; furthermore RPE cells showed an increased production of tumor necrosis factor α (TNFα) and IL-1 [16] recruiting macrophages accounting for the inflammatory component of CNV, and also IL-2, IL-6, and IL-10 have been found, but their role is not clear yet [17].

Other mediators play a role in the membrane development: nitric oxide that induces the membrane formation, besides angiostatin, endostatin, CCR3, and the pigment epithelium derived growth factor (PEDF) contrasting the neovascularization. Focally the membrane can become fibrous and it is thought that the transforming growth factor β (TGF-β) is responsible for the process of recruiting choroidal fibroblasts, but on the other hand, at the same time, it induces the production of VEGF leading to the formation of new active foci [18].

4. Therapy and Clinical Studies

Understanding the uveitis as better as possible and identifying underlying infectious diseases are mandatory in order to keep the inflammation under control using the correct medical therapy. The use of steroids and immunosuppressors [19] has shown some utility in preventing and, sometimes, stopping the development of inflammatory CNV, but in the new millennium innovative therapies for ARMD came out and thus were tried on the inflammatory counterpart, leaving argon laser ablation, surgical membrane removal, and macular translocation a marginal role. But the uveitic subretinal membrane is less frequent than the wet ARMD, so researchers cannot freely design comparative studies.

In the literature most of clinical studies on inflammatory CNV therapy are case series with few underpowered retrospective studies often uncontrolled. Commonly patient selection was done in many different ways (naive/treated patients, active/quiescent uveitis, adult/pediatric, and different systemic therapy), making any attempt of rigorous meta-analysis impossible. We focused on the three main therapies available in the last decade: (i) photodynamic therapy (PDT), (ii) intravitreal bevacizumab (IVB), and (iii) intravitreal ranibizumab (IVR). We selected most important published articles in the last ten years with more than 2 subjects and, where possible, we extracted the data of patients. In Table 2 we report the name of the first author and the year of publication,

Table 1: *P* values of Mann-Whitney test performed on the dataset from Guerin et al. [14] comparing the staining grading for the three molecules studied (SDF1, CXCR4, and VEGFR-2) of the three structures of a CNV.

	SDF1			CXCR4			VEGFR-2		
	RPE	Vascularization	Fibroblasts	RPE	Vascularization	Fibroblasts	RPE	Vascularization	Fibroblasts
Inflammation versus ARMD	0.92	0.63	0.63	0.92	0.074	0.19	0.41	0.92	0.92

Table 2: Overview of the studies on the therapy of inflammatory CNV.

Study (year) [reference]	Uveitis type	FU	PDT	Bevacizumab (median numbers of injections)	Ranibizumab (median numbers of injections)
Saperstein et al. (2002) [20]	POHS	12	21/25		
Spaide et al. (2002) [21]	MC	10	7/7[§]		
Rogers et al. (2003) [22]	MISC	12	8/9[§]		
Wachtlin et al. (2003) [23]	MISC	22	17/19		
Nessi et al. (2004) [24]	TOXO	3	2/3[§]		
Leslie et al. (2005) [25]	MISC	11	6/6[§‡]		
Parodi et al. (2006) [26]	MC	12	6/7		
Coco et al. (2007) [27]	PIC	23	5/8[§]		
Gerth et al. (2006) [28]	MISC	23	7/14[§]		
Lim et al. (2006) [29]	MISC	12	3/5		
Mauget-Faÿsse (2006) [30]	TOXO	25	6/8		
Nowilaty and Bouhaimed (2006) [31]	VKH	19	4/6[§‡]		
Adán et al. (2007) [32]	MISC	7		8/9 (1)	
Chan et al. (2007) [33]	PIC	6		4/4 (3)	
Schadlu et al. (2008) [34]	POHS	6		26/28 (1.8*) most pts. had PDT	
Priyanka et al. (2009) [35]	MISC	15		4/6 (3)[§]	
Tran et al. (2008) [36]	MISC	6		10/10 (2.5)[§‡]	
Fine et al. (2009) [37]	MC	6		4/5 (1.5)	
Lott et al. (2009) [38]	MISC	7		15/21 (2)[§‡]	
Parodi et al. (2010) [39]	MC	12	9/13	12/14 (3.8*)	
Ehrlich et al. (2010) [40]	MISC	9	4/4[§]		
Kramer et al. (2010) [41]	MISC	12		10/10 (2)[§]	
Menezo et al. (2010) [42]	PIC	12			8/9 (1)[§]
Arevalo et al. (2011) [43]	MISC	12		21/23 (1)	
Carneiro et al. (2011) [44]	MISC	6			4/5 (3)
Cornish et al. (2011) [45]	PIC	12		5/6 (2)	2/3 (4)
Julián et al. (2011) [46]	MISC	15		12/15 (4.25*)[§‡]	
Rouvas et al. (2011) [47]	MISC	17			16/16 (2)
Troutbeck et al. (2012) [48]	MC	12			6/7 (3.4*)
Iannetti et al. (2013) [49]	MISC	19		7/8 (1)[§]	
Mansour et al. (2012) [50]	MISC	36		67/81 (3)	
Totals (median no of inj.) Percentual of success			105/134 78.4%	138/159 (2) 86.8%	36/40 (3) 90.0%

The first column shows the first author name, year of publication, and the reference in square brackets; the second column shows the type of uveitis studied (POHS: presumed ocular histoplasmosis, MC: multifocal choroiditis, MISC: miscellaneous, TOXO: toxoplasmosis, PIC: punctuate inner choroidopathy, and VKH: Vogt-Koyanagi-Harada disease); the third column shows the median follow-up calculated from dataset where not available; in the fourth, fifth, and sixth columns we reported the number of eyes whose VA stabilized or improved with the therapy over the number of eyes treated, respectively, for PDT, IVB, and IVR. Also we indicated the median numbers of injections needed or the mean number* if reported in the study. In the cells [‡]indicates more than half patients had immunosuppressive treatment or [§]for steroid therapy. The last row shows the number of cumulative successes in the eyes treated and the relative percentages. Further statistical analysis was impossible due to the extreme heterogeneity of the studies.

the uveitis type included in the study, the median follow-up, where available or calculable, or the median follow-up time as provided in the paper. Moreover, we reported the number of subjects that after the treatment did not lose any line/letter on the total of patients, divided into three columns, one for each therapy, and the median numbers of injections performed or the mean numbers of injections if reported in the study. The articles are ordered by year of publication and then for first author name; at the end of the table we reported the sum and the percentages of success for each therapy in terms of visual acuity (VA) improvement and stabilization. We chose not to perform any statistical analysis on the data because such wide difference between the background studies could give highly biased results. Some well-known articles are not included because we could not extract the data about inflammatory patients only (as in Chang et al.) or because the dataset of patients resembled one of the other published articles by the same group of study.

The first articles report the case series on the PDT; overall success rate is quite high (78.4%) compared to previously reported significative vision loss in untreated patients (77% VA below 20/100) [51]. In most of these studies local or systemic steroid therapy was associated, and in two of them [25, 31] immunosuppressive drug was used in the majority of patients. Subsequently in the following years, the use of anti-VEGF therapy increased and IVB became available; 12 case series and 2 comparative retrospective studies about the IVB treatment in uveitis-related CNV are reported (Lott et al. [38] and Cornish et al. [45]). The first compares PDT to IVB in MC and the second IVB to IVR in PIC, but only in few cases. The work of Battaglia-Parodi did not show differences in overall success rate between the two therapies but showed a better visual recovery in patients treated with IVB. The final success rate for IVB seems to be around 87%. Finally in recent years IVR became more used, partly because of the concerns of the off-label use of IVB. We found the final success rate of the latter therapy to be around 90%, not very different by IVB treatment.

Although more than 30 articles were published about the argument, a decision about the treatment of inflammatory CNV cannot be assessed on evidence based medicine, as case series and uncontrolled studies are in the lower half of the scale of scientific evidences. Thus, well-designed randomized clinical trials should be necessary, but a correct comparison between the three main therapeutic strategies would need studies with a large number of people, which is not feasible for a rare complication of a rare disease such as posterior uveitis with strict inclusion and exclusion criteria.

A wise therapeutic approach we may suggest is the following:

(i) thorough control of the underlying inflammation using steroids, immunosuppressors, or specific treatment where appropriate;

(ii) use of PDT for early extrafoveal lesions not causing a decrease in the VA, a less invasive procedure is always preferable in a uveitic eye in order to keep the possibility of flogosis reactivation low;

(iii) use of IVR for foveal or juxtafoveal membranes or as second line therapy after PDT, the paper of Battaglia-Parodi demonstrated a higher VA for the IVB, but this drug is currently off-label for intravitreal use, and we could expect similar efficacy. Furthermore the literature showed that inflammatory CNV needs much less intravitreal injection than ARMD-related CNV to achieve the complete regression of the membrane.

Every year there is the announcement of new therapeutic approaches for wet ARMD, aflibercept, and stereotactic radiotherapy as examples, and the treatment of inflammatory CNV will benefit from these news although again it will be difficult to obtain a specific randomized controlled trial, so necessarily we will have to rely on indirect data.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Emerging Therapies for Noninfectious Uveitis: What May Be Coming to the Clinics

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Corticosteroids along with other immunomodulatory therapies remain as the mainstay of treatment tor all patients with noninfectious uveitis (NIU). However, the systemic side effects associated with the long-term use of these drugs has encouraged the development of new therapeutic agents in recent times. This review article discusses upcoming therapeutic agents and drug delivery systems that are currently being used to treat patients with NIU. These agents mediate their actions by blocking specific pathways involved in the inflammatory process. Agents discussed in this review include full or recombinant monoclonal antibodies against interleukins such as IL-17 (secukinumab), IL-l (gevokizumab), and IL-6 (tocilizumab and sarilumab), antibody fragments against inflammatory cytokines such as TNF-α (ESBA 105) and T-cell inhibitors such as fusion proteins (abatacept), and next generation calcineurin inhibitors (voclosporin). In addition, administration of immune modulatory therapies using methods such as iontophoresis (EGP-437) and intravitreal injection (sirolimus) for the treatment of NIU' uveitis has also been discussed.

1. Introduction

Local and systemic corticosteroids are the mainstay of treatment for all patients with noninfectious uveitis (NIU); however, long term use of steroids can lead to both systemic and local adverse effects, such as cataracts, glaucoma, and metabolic disorders, among several others [1]. Increasing efforts are being made to develop a treatment option that will limit corticosteroid use and, therefore, decrease the risk of its associated adverse effects. Current guidelines recommend the addition of immunomodulatory therapy (antimetabolites, calcineurin inhibitors, alkylating agents, and tumor necrosis factor- (TNF-) alpha inhibitors) when inflammation cannot be controlled with ≤10 mg/day of prednisone within three months. Although this approach decreases the risks associated with corticosteroid use, immunomodulatory therapy (IMT) in itself has been associated with toxicities and has limited efficacy in some patients, further highlighting the need for a safer alternative to corticosteroids [2].

The index review article focuses primarily on the new therapeutic options for NIU, including novel agents and established drugs with innovative delivery systems.

2. Therapies in Development

2.1. AIN457 (Secukinumab). IL-17 was first identified in rodent T-cell hybridoma and subsequently cloned in CD4 + T-cells in 1995. IL-17 is produced by TH17 cells and mediates its actions through a heterotrimeric receptor composed of two IL-17RA subunits and one IL-17RC subunit, consequently promoting the expression of antimicrobial peptides and inducing secretion of proinflammatory cytokines, chemokines, and metalloproteinases. New evidence suggests IL-17 activity in immune protection against parasites and viruses; however, in contrast to its protective role, it can also lead to adverse effects that result in tissue damage associated with various human inflammatory diseases such as rheumatoid arthritis (RA), psoriasis, multiple sclerosis

(MS), and inflammatory bowel disease (IBD) [3]. Likewise in uveitis, the upregulation of IL-17A in patients with active Adamantiades-Behçet and Vogt-Koyanagi-Harada (VKH) diseases has led to the targeting of this interleukin in ocular inflammatory diseases [4, 5].

By blocking the pathogenic driver IL-17A, the fully human antibody AIN457 (Novartis Pharmaceutical, Basel, Switzerland) has been shown to interrupt inflammation in patients with RA, psoriasis, and NIU [6]. In an open label study of the safety and tolerability of secukinumab, 16 patients with active chronic NIU were treated with two infusions of AIN457 (10 mg/kg), at baseline and 3 weeks later. The majority of patients responded with a rapid reduction in vitreous haze that was sustained in the following 8 weeks with an increase of visual acuity (VA). No serious adverse events were reported [6]. Following the results of this study, further clinical trials have been initiated to evaluate the efficacy and safety of secukinumab in NIU. Dick et al. recently reported a significant reduction in mean total postbaseline immunosuppressive medication (ISM) scores with no loss in visual acuity (VA) in patients treated with AIN457 for NIU. However, the primary endpoint of the study, that is, the uveitis recurrence in patients receiving secukinumabcompared to the placebo group, was not statistically significant in any study. Secukinumab was associated with a significant reduction in mean total postbaseline ISM score ($P = 0.019$; 300 mg q4w versus placebo) in the SHIELD study.

Likewise, secukinumab was associated with a greater median reduction in ISM score versus placebo in the INSURE study, although no statistical analysis of the difference was conducted because of the small sample size. Overall, there was no loss in visual acuity reported in any treatment group during follow-up in all 3 studies. According to descriptive safety statistics, the frequencies of ocular and nonocular adverse events seemed to be slightly higher among secukinumab groups versus placebo across the 3 studies [13] (Table 1).

2.2. DE-109 (Sirolimus). *Sirolimus* (Santen Pharmaceutical, Osaka, Japan) is a macrolide antibiotic produced naturally by *Streptomyces hygroscopicus,* isolated in soil samples from Easter Island. Although originally developed as an antifungal agent, sirolimus has a potent immunosuppressive and antineoplastic activity that depends upon its binding to specific cytosolic proteins (immunophilins) to generate an immunosuppressive complex (RAPA : FKBP). FKBP-12 is the most relevant immunophilin that inhibits the activation of the mammalian target of rapamycin (mTOR) resulting in the suppression of the cytokine driven T-cell proliferation by blocking and inhibiting several signal transduction pathways (phosphorylation and activation of p70-S6 kinase1 and phosphorylation and inactivating 4E-BP1) [7]. The inhibition of the proliferation of B-cell lymphocytes and IL-2, IL-4, and IL-5 represents other additional immunomodulatory effects of rapamycin.

Clinically, the safety profile of this agent has been studied in other ocular conditions including dry eye syndrome, age-related macular degeneration (AMD), and diabetic macular edema (DME) [14, 15]. Initial studies for uveitis reported that systemic sirolimus was effective in the majority of refractory NIU cases, improving the signs and symptoms of inflammation and reducing the steroid burden. However, the systemic/intravenous route of administration was associated with side effects and/or failure to control uveitis in some patients [16, 17]. The Sirolimus as Therapeutic Approach to Uveitis (SAVE) study evaluated the safety end efficacy of sirolimus administered as a subconjunctival or intravitreal injection in patients with NIU results of this study did not find statistically significant differences in bioactivity between the two study groups at month 6, with both subconjunctival or intravitreal injections showing an improvement of two steps or more in vitreous haze in approximately 40% of the patients [18]. Other clinical trials, including Intravitreal Sirolimus as Therapeutic Approach to Uveitis—Phase 2 (SAVE-2), which is being coordinated by the Ocular Imaging Research and Reading Center at the Truhlsen Eye Institute of the University of Nebraska Medical Center, and The Study Assessing Double-masked Uveitis Treatment (SAKURA), will help to establish the long-term safety and efficacy of local ocular formulation of sirolimus in the future (Table 1).

2.3. XOMA 052 (Gevokizumab). Gevokizumab (XOMA Corporation, Berkley, CA, USA) is a recombinant humanized IgG2 antibody that binds strongly to Interleukin-1β (IL-1β), thereby preventing activation of the IL-1 receptor [9]. The chronic inflammation in islet cells in patients with type 2 diabetes has been associated with the pathological activation of (IL)-1. A phase 2 study was conducted in 2007 in order to evaluate the safety and biological activity of gevokizumab in patients with type II diabetes. Results of this study showed a significant decrease in C-reactive protein (CRP) and an improvement in glycemic control [19].

A pilot study conducted by Gül et al. in 2012 showed that the recombinant, humanized anti-IL1β antibody, XOMA 052, incited a rapid and sustained reduction in inflammation in seven refractory NIU (Adamantiades-Behçet disease) patients. This effect was observed without the need to increase the dose of corticosteroids, despite the discontinuation of other immunomodulatory therapies [20].

Following the results of the initial study, three phase III studies, EYEGUARD-A (for patients with active disease), EYEGUARD-B (for patients with Adamantiades-Behçet's disease), and EYEGUARD-C (for patients with controlled disease), have been initiated [21]. In these studies, subjects receive three monthly injections of gevokizumab (60 mg) followed by an extended assessment phase of the study that will last 36 weeks after completion of the study. The primary outcome is the number of participants with at least two-step reduction in vitreous haze or a reduction to zero in scleral inflammation before or at week 16 (Table 1).

In addition, a phase II open label clinical trial in patients with active noninfectious anterior scleritis is also being conducted with gevokizumab [22].

2.4. ESBA105. ESBA105 (Alcon Research, Hünenberg, Switzerland) is a topically administrated antibody fragment

Table 1: Clinical trials for emergent therapies in noninfectious uveitis.

Drug	Mechanism of action	Study name phase	Sample size	Intervention	Results
AIN457 secukinumab (SK)	Fully humanized antibody blocks IL-17A [6]	SHIELD Phase III	118	(i) SK 300 mg s.c. at baseline, week 1 and week 2 (loading phase), and then every 2 weeks (ii) SK 300 mg s.c. loading phase and then monthly (iii) Placebo s.c. loading phase and then every 2 weeks	(i) Greater reduction in mean total postbaseline composite immunosuppressive medication (ISM) in the SK group compared with placebo ($P = 0.047$) (ii) No statically significant differences in change in BCVA between the SK group and placebo (iii) Median decrease in vitreous haze was similar among treatment groups
		INSURE Phase III	31	(i) SK 300 mg s.c. loading phase and then every 2 weeks (ii) SK 300 mg s.c. loading phase and then monthly (iii) SK 150 mg s.c. loading phase and then monthly (iv) Placebo s.c. loading phase and then every 2 weeks	(i) No major differences in mean change in vitreous haze from baseline to week 28 in all groups (ii) ISM score 0.0 for all SK groups, 1.83 for placebo (iii) No loss in BCVA in all the groups (iv) No apparent dose-response relation for the incidence of AEs (adverse events)
		ENDURE Phase III	125	(i) SK 300 mg s.c. loading phase and then every 2 weeks (ii) SK 300 mg s.c. loading phase and then monthly (iii) SK 150 mg s.c. loading phase and then monthly (iv) Placebo s.c. loading phase and then every 2 weeks	(i) No statistically significant differences between all the groups in the time of first recurrence of uveitis (ii) Composite ISM score is similar across all the groups
DE-109 sirolimus	mTOR inhibitor [7]	SAVE Phase I	30	(i) Intravitreal sirolimus: 325 μg at days 0, 60, and 120 (ii) Subconjunctival injection: 1320 μg at days 0, 60, and 120	(i) Did not find statistically significant differences between the two study groups at month 6 (ii) improvement of two steps or more of vitreous haze in 40% of the patients
		SAVE-2 Phase II	30	(i) Intravitreal sirolimus 440 μg at baseline and months 1, 2, 3, 4, and 5 and then prn after month 6 (ii) Intravitreal sirolimus 880 μg at baseline and months 2 and 4 and then prn after month 6	Recruiting
		SAKURA Phase III	500	(i) Sirolimus low dose (44 μg) intravitreal (ii) Sirolimus medium dose (440 μg) intravitreal (iii) Sirolimus high dose (880 μg) intravitreal	Recruiting

Table 1: Continued.

Drug	Mechanism of action	Study name phase	Sample size	Intervention	Results
EGP-437 iontophoresis dexamethasone phosphate	Glucocorticoid receptor antagonist [8]	Phase I/II	40	(i) 1.6 mA-min (ii) 4.8 mA-min (iii) 10 mA-min (iv) 14 mA-min	(i) By day 28, 40 patients (60%) achieved an anterior chamber cell score of zero (ii) 1.6 mA-min was the most effective dose (iii) Intraocular pressure and BCVA remained stable throughout the study
XOMA 052 gevokizumab	Recombinant humanized anti-IL1β antibody [9]	EYEGUARD A Active Uveitis Phase III		(i) Placebo drug s.c. (ii) Group 1 gevokizumab s.c. (iii) Group 2 gevokizumab s.c.	Recruiting
		EYEGUARD C Controlled Uveitis Phase III		(i) Placebo drug s.c. (ii) Dose 1 gevokizumab s.c. (iii) Dose 2 gevokizumab s.c.	Recruiting
Abatacept (Orencia)	CD28 inhibitor [10]	Abatacept in the Treatment of Noninfectious Uveitis Phase II	20	(i) Abatacept 10 mg/kg for the first 6 months (ii) At month 6 randomization to receive either 5 mg mg/kg or 10 mg/kg	Recruiting
Tocilizumab	IgG1 recombinant humanized antihuman monoclonal antibodies that target IL-6 receptors [11, 12]	STOP Uveitis Phase I-II	36	(i) Tocilizumab 4 mg IV, 6 monthly doses, and then prn after month 6 (ii) Tocilizumab 8 mg IV 6 monthly doses, and then prn after month 6	Recruiting
Sarilumab		Study to Analyze Sarilumab in Noninfectious Uveitis Phase II	57	(i) Sarilumab s.c. every 2 weeks up to 50 weeks (ii) Placebo s.c. every 2 weeks up to 50 weeks (iii) In both groups prednisone as single therapy or in combination with methotrexate are continued	Recruiting

against TNF-α [23]. In 2009, Ottiger et al. discovered that, even without the use of therapeutic enhancers, it could penetrate into the anterior and posterior chambers at therapeutic levels by translimbal/intrascleral migration [24].

Clinically, the safety and the efficacy of topical administration of ESBA105 were reported in a study of 57 patients who were scheduled for surgery (cataract or vitrectomy); the study reported that topical administration of ESBA105 rapidly achieved high intraocular levels, maintaining a favorable safety and tolerability profile [25]. A pilot study of ESBA105 applied hourly followed by dose tapering was completed in patients with acute anterior uveitis; however, the results of this study are currently not available [26].

2.5. Abatacept (Orencia). T-cell antigen CD28 provides a costimulatory signal needed for T-cell activation; such cascade results in T-cell proliferation and secretion of several lymphokines including interleukin-2 (IL-2). CD28 signaling is triggered by its counter receptors, CD80 and CD86, which are expressed on antigen-presenting cells (APC). Orencia (Bristol-Myers Squibb Company, New York, USA) is a CTLA4-IgG fusion protein that targets CD80/CD86 and consequently blocks T-cell activation [10].

Abatacept has been used in Th-1 mediated diseases such as psoriatic arthritis, juvenile idiopathic arthritis (JIA), and RA [10, 27]. In 2010, Zulian et al. found that Orencia initiated and sustained well-tolerated improvement in refractory cases of psoriatic and JIA-associated anterior uveitis [28]. An open label phase II uveitis study is currently recruiting patients with refractory and vision-threating uveitis [29].

2.6. Tocilizumab (Actemra; Roche, Nutley, New Jersey, USA) and Sarilumab (Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, and Sanofi, Paris, France). Interleukin-6 (IL-6) is a pleotropic cytokine produced by T-cells, B-cells, monocytes, fibroblasts, synovial cells, and endothelial cells. It has a wide range of biological activities and is a key player in the pathogenesis of numerous inflammatory disorders such as RA. IL-6 binds to either a transmembrane receptor (mIL-6R) or to a soluble receptor (sIL-6R) formed by the proteolytic cleavage of mIL-6R. After binding to the receptor, IL-6 recruits two molecules of the transducing glycoprotein (gp130) involved in the down-stream signaling process. Signaling by the sIL-6R is a key feature in the pathophysiology of autoimmune diseases and chronic inflammation rather than the mIL-6R. Neutralizing monoclonal antibodies against this pathway are currently under investigation [11].

Tocilizumab (Actemra; Roche, Nutley, New Jersey, USA) and sarilumab (Regeneron Pharmaceuticals, Inc., Tarrytown, NY USA) are humanized antihuman monoclonal IgG1 antibodies synthesized by recombinant DNA technology that target both IL-6 receptors, thereby blocking the proinflammatory effects of IL-6 [11, 12]. TCZ is currently approved in the USA for RA, particularly in treatment refractory cases. The STOP-UVEITIS study, a multicentered clinical trial investigating the safety, efficacy, and bioactivity of different doses of TCZ in patients with NIU, has been initiated in 2012 in the US and is being coordinated by the Ocular Imaging Research and Reading Center at the Truhlsen Eye Institute of the University of Nebraska Medical Center. In addition, a multicentered study investigating the efficacy and safety of sarilumab in patients with NIU (the SATURN Study) is also currently underway at various sites in Europe and United States. The SATURN Study is sponsored by Sanofi in collaboration with Regeneron Pharmaceuticals (Table 1).

2.7. EGP-437 (Iontophoretic Dexamethasone Phosphate). EGP-437 (Eyegate Pharmaceuticals, MA, USA) is a dexamethasone phosphate solution that is delivered to the eye via iontophoresis, a technique first reported in 1943 by von Sallman et al. Iontophoresis consists of applying a current in a controlled manner, by an ocular applicator, for producing ions (hydroxide or hydronium) that drive the drug molecule noninvasively into the anterior and posterior segments of the eye, thereby minimizing the systemic distribution of the drug. Dexamethasone phosphate is a dexamethasone prodrug that is highly water soluble with a buffering ability necessary for iontophoresis [8].

Clinically, EGP-437 has been shown to have prolonged duration of action and has proved to be significantly more effective compared to other delivery routes, such as the topical and subconjunctival route [8, 30]. In 2012, Cohen et al. in a phase I/II study reported that EGP-437 was well tolerated and extremely effective, achieving anterior cell chamber scores of 0 within 28 days after just one treatment in 60% of participants with noninfectious anterior uveitis [8]. Based on these findings, a phase III study comparing ECGP-437 (4-mA/min) with topical prednisolone acetate (1%) to treat noninfectious anterior uveitis was initiated and has been completed recently; the primary outcome in this study will be the percentage of patients with an anterior chamber score of 0 at day 14.

Beyondthe studies on anterior uveitis, a pilot study evaluating the safety of EGP-437 in patients with anterior scleritis has been conducted. Study subjects were randomized to receive either EGP-437 or sham treatment. Dose-limiting toxicity was the primary outcome of this study. The results of this study are awaited [31].

2.8. LX211 (Voclosporin). Voclosporin (Lux Biosciences, Jersey City, NJ, USA) is an orally active next-generation calcineurin inhibitor with potent immunosuppressive activity. Inside the lymphocyte, this molecule forms a complex with immunophilins consequently inhibiting calcineurin. This action prevents the translocation of the cytoplasmic component of the activated T-cells to the nucleus, resulting in impaired transcription of the genes encoding IL-2, a molecule essential for T-cell proliferation and other inflammatory lymphokines [32].

Voclosporin has a structure that is similar to cyclosporine-A, except for a modification in the amino acid-1 residue, which gives the molecule a higher binding affinity for calcineurin and a more predictable pharmacokinetic profile [32].These characteristics allowed this agent to be an invaluable immunosuppressant in organ transplantation and other autoimmune conditions such as RA and psoriasis

[33]. During the past few years, attention has been gained on Th-1 mediated conditions like dry eye syndrome and uveitis. The Lux Uveitis Multicenter Investigation Clinical Program (LUMINATE) was developed to demonstrate the usefulness of voclosporin in patients with active or quiescent posterior uveitis or active anterior uveitis. The results of this study in active posterior uveitis demonstrated a reduction in the vitreous haze in 50% of patients and prolonged the time to recurrence by twofold, while in quiescent uveitis, it reduced the frequency of exacerbations by 50%. In all the study groups, the reduction in the burden of oral prednisolone doses to ≤5 mg/d was reported in 96%–98% of the patients. The results for this drug have so far been comparable to current therapeutic options, with the added benefit of a better safety profile and possibly a better compliance due to its oral route of administration. However, a second phase III trial did not show a statistically significant difference between the placebo and disease groups. No additional studies are planned at this time to evaluate this agent further.

3. Conclusion

The management approaches for patients with uveitis are protean and challenging, given the complexity of the pathophysiology of the disease. Clinical recommendations for the treatment of uveitis include a no tolerance policy for any degree of inflammation together with an acceptable dose of corticosteroids (<7.5 mg/day). Such therapeutic principles and algorithm have led to an extensive search for novel immunomodulatory therapies (IMT), in terms of the mechanism of actions or mode of delivery, that would halt or reduce the degree of inflammation in patients with uveitis and, therefore, provide control of the disease and reduce the need for steroid therapy. However, in a number of patients treated with IMT, the treatment is either suboptimal or causes undesirable side effects. An increased understanding of the human immune system in recent times has led to the development of potentially new agents that target the disease pathways in a more effective manner, thereby helping to combat this sight-threatening disease. It is hoped and expected that these potential pharmacologic agents may be used in combination, even with low dose corticosteroids, to provide multimodal and multitargeted control of the inflammatory process.

Disclosure

Dr. Quan Dong Nguyen chairs the steering committee for the SAKURA Study and the VISUAL Study. He also serves on the scientific Advisory Boards for Santen, Abbvic, XOMA, Bausch and Lomb, and XOMA.

Conflict of Interests

All authors except Quan Dong Nguyen declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Ischemic Retinal Vasculitis and Its Management

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Ischemic retinal vasculitis is an inflammation of retinal blood vessels associated with vascular occlusion and subsequent retinal hypoperfusion. It can cause visual loss secondary to macular ischemia, macular edema, and neovascularization leading to vitreous hemorrhage, fibrovascular proliferation, and tractional retinal detachment. Ischemic retinal vasculitis can be idiopathic or secondary to systemic disease such as in Behçet's disease, sarcoidosis, tuberculosis, multiple sclerosis, and systemic lupus erythematosus. Corticosteroids with or without immunosuppressive medication are the mainstay treatment in retinal vasculitis together with laser photocoagulation of retinal ischemic areas. Intravitreal injections of bevacizumab are used to treat neovascularization secondary to systemic lupus erythematosus but should be timed with retinal laser photocoagulation to prevent further progression of retinal ischemia. Antitumor necrosis factor agents have shown promising results in controlling refractory retinal vasculitis excluding multiple sclerosis. Interferon has been useful to control inflammation and induce neovascular regression in retinal vasculitis secondary to Behçet's disease and multiple sclerosis. The long term effect of these management strategies in preventing the progression of retinal ischemia and preserving vision is not well understood and needs to be further studied.

1. Background

Retinal vasculitis is a sight-threatening inflammatory condition, occurring in approximately one in every eight eyes with uveitis [1]. Based on the etiology, retinal vasculitis may be classified as either idiopathic or secondary to infection, neoplasia, or a systemic inflammatory disease [2, 3]. In a cohort study involving 1390 patients with uveitis, 15% had retinal vasculitis as part of their uveitic manifestations [1]. The main concern with retinal vasculitis is the risk of developing vasooclusion and retinal ischemia that can lead to serious sight threatening manifestations. In a retrospective study of 113 eyes with retinal vasculitis in eastern India, capillary nonperfusion was the most common fundus fluorescence angiography (FFA) finding seen in retinal vasculitis, found in 40% of the cases, followed by collateral vessels, seen in 19.5% of eyes with vasculitis [4]. Different causes of retinal vasculitis carry variable risks of developing retinal ischemia ranging from being common in presumed tuberculous retinal vasculitis and Behçet's disease to a more rare association in sarcoidosis and multiple sclerosis (Table 1) [3, 5].

The pathogenesis of ischemia in retinal vasculitis is not clear but is suggested to be either thrombotic or obliterative secondary to the infiltration of inflammatory cells (Figure 1). Based on histological studies, vascular changes in uveitis are characterized by perivascular infiltration of lymphocytes resulting in perivasculitis rather than a true vasculitis of the vessel wall [6, 7]. Cell-mediated immunity also plays a role in the pathology of retinal vasculitis, with CD4+ T cells documented within and around the retinal vessels. Thrombotic vascular changes can occur due to local endothelial injury or increased prothrombin activity as observed in Behçet's disease [8]. The retina has a uniquely high metabolic demand for oxygen that is normally met by a highly efficient vascular supply. Insufficiency of the retinal circulation causes neuroretinal dysfunction and degeneration. Focal retinal ischemia results in selective damage to specific subpopulations of retinal neurons and can result in cellular death by apoptosis or necrosis with dysfunction and degeneration of the inner retina and eventually visual loss. Retinal vascular obstruction can also promote the production of vascular endothelial growth factor (VEGF), which increases vascular

Table 1: Cause of retinal vasculitis according to the type of vessels involved and association with retinal ischemia.

	Mainly involve arteries	Mainly involve veins	Associated with retinal ischemia
Infectious disorders	Acute retinal necrosis Toxoplasmosis Cat scratch disease West Nile virus	Tuberculous hypersensitivity Syphilis CMV HIV Rift Valley fever virus HTLV-1	Tuberculous hypersensitivity West Nile virus
Noninfectious disorders	SLE APHA Takayasu's disease IRVAN GPA Churg-Strauss syndrome Crohn's disease Polyarteritis nodosa Susac syndrome Dermatomyositis	Behçet's disease Sarcoidosis Multiple sclerosis Birdshot chorioretinopathy APMPPE Pars planitis HLAB27 associated uveitis	Behçet's disease Sarcoidosis Multiple sclerosis SLE APHA Takayasu's disease IRVAN GPA Dermatomyositis Churg-Strauss syndrome Crohn's disease Polyarteritis nodosa Susac syndrome Idiopathic retinal vasculitis

SLE: systemic lopus erythematosus; APHA: antiphospholipid antibody syndrome; IRVAN: idiopathic retinal vasculitis, arteriolar macroaneurysms, and neuroretinitis; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HTLV-1: human T-cell lymphoma virus type 1; APMPPE: acute posterior multifocal placoid pigment epitheliopathy; GPA: granulomatosis with polyangiitis.

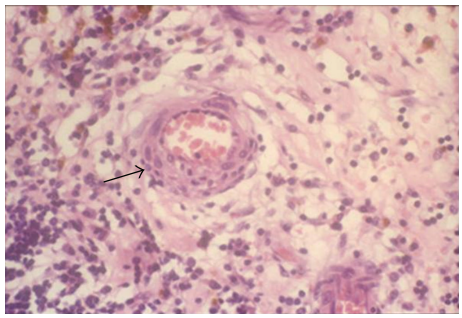


Figure 1: Histopathological image of a retinal blood vessel involved in Behçet's disease (H & E stain). Note the perivascular infiltration of lymphocytes around the vessel (arrow).

permeability and results in macular edema and induced neovascularization [9].

The management and long term outcomes of ischemic retinal vasculitis as a whole have rarely been addressed in prospective studies. In one retrospective study, 20 patients (38 eyes) with ischemic retinal vasculitis were compared to 33 patients (62 eyes) with nonischemic vasculitis. While the initial visual acuity was not significantly different between the two groups, 13 (34%) eyes in the ischemic group had final severe visual loss compared with 4 (6%) eyes in the nonischemic group and no significant difference in the median number of relapses/year between both groups [10]. The risk of visual loss in cases with retinal ischemia relates to involvement of posterior pole as in macular edema and macular ischemia or due to stimulating neovascularization (NV) at optic disc (NVD) or elsewhere in the retina (NVE). These fragile new vessels bleed easily resulting in vitreous hemorrhage (VH), fibrovascular proliferation, and subsequent tractional retinal detachment. While the NV itself is managed mainly using scattered laser photocoagulation (SLP) to the ischemic area, the role of immunosuppressive/immunomodulatory (IMS) medications in preventing further progression of retinal ischemia is not fully understood.

2. Presumed Tuberculous Retinal Vasculitis

Ischemic retinal vasculitis may be secondary to tuberculous infection (TB) or as a result of a hypersensitivity reaction to tuberculoprotein. In a clinical review of 21 patients with presumed ocular TB infection, occlusive retinal vasculitis was the most common presentation affecting 12 patients, of which eight (38%) had underlying active systemic TB [11]. In another study on 73 eyes (51 patients) with presumed TB uveitis, the authors found retinal periphlebitis in 35% of eyes involved. This was complicated by NV in 29% (half seen on presentation), VH in 11%, and retinal detachment in 3% of eyes [12].

Possible mechanisms resulting in venous occlusion include disc edema secondary to tuberculous inflammation or obliteration of the vessels by a hypersensitivity reaction to *M. tuberculosis*. In these cases, occlusive periphlebitis can affect the retina in multiple quadrants and is associated with thick exudates around the retinal veins and retinal hemorrhages. As a consequence to retinal ischemia, NV, VH, traction retinal detachment, rubeosis iridis, and neovascular

glaucoma can occur [5]. CRVO has also been reported [13, 14] and may be associated with retinal vasculitis, chorioretinitis, and retinal ischemia. In one case, the inflammation resolved gradually following the initiation of anti-TB therapy, while intravitreal bevacizumab therapy given one month after presentation had little effect with VH occurring five months after the injection [14]. Presumed TB retinal vasculitis can result in extensive peripheral capillary closure with recurrent VH in young adult males, in the absence of other features of intraocular inflammation such as vitreous cells. In other cases, active or healed patches of focal choroiditis along the retinal veins can help to differentiate presumed TB vasculitis from other causes of retinal vasooclusion (Figure 2) [15].

3. Behçet's Disease

Ocular involvement in Behçet's disease (BD) occurs in approximately 70% of the patients and is associated with a high risk of visual loss [16, 17]. In a retrospective study of 107 patients with ocular BD, the 10-year risk of developing severe visual loss of 6/60 or worse was 13% and ischemic maculopathy secondary to BRVO was attributed to half the cases of irreversible severe visual loss [18]. The contribution of BD on the overall incidence of retinal vasculitis can vary based on the population at risk. A review of 1390 uveitis cases on the west coast of the United States found 207 patients with evidence of retinal vasculitis; of these cases, only 14 patients had BD [1]. On the other hand, retinal vasculitis is common among patients with ocular BD. In one multicentre study, 22% of eyes with ocular BD had retinal vasculitis [16].

Retinal vasculitis in ocular BD most commonly manifests as vitritis with diffuse vascular leakage on FFA due to inflammatory hyperpermeability. This may be accompanied by capillary nonperfusion secondary to occlusive vasculitis resulting in NV. Both retinal arteries and veins can be involved in BD though venous involvement is more common [3]. BRVO with intraretinal hemorrhages and macular edema are frequently seen and these are often central in the retinal with a high risk of significant visual loss (Figure 3). BRVO and ischemic retinal vasculitis have been reported as the first presentation of ocular BD in 28% and 21%, respectively, while central vein (4%) and artery (1%) occlusions are less common presentations [18]. Macular ischemia, a predictor of poor visual outcome, has also been reported in cases with BD. In a recent retrospective study of 120 eyes of patients with BD, macular ischemia was seen in one eye (0.8%) at initial visit, while three eyes (2.5%) developed ischemia during a mean follow-up period of 22 months [19]. NV is a serious complication observed by one study in 4% of 1567 eyes with Behçet's uveitis [20], and a multicentre study reported an incidence rate of 0.12 to 0.17 per person per year [16]. NV in BD can be secondary to inflammation and regress in response to IMS therapy or present as an early complication of Behçet's uveitis even in the absence of retinal ischemia [21].

4. Systemic Lupus Erythematosus

The incidence of retinopathy in patients with systemic lupus erythematosus (SLE) ranges from 3% to 29% [22–24] depending on the studied population and associated risk factors for SLE retinopathy such as the presence of anticardiolipin antibodies, central nervous system involvement, serum creatinine level, and SLE activity [22, 25]. Retinal vasculopathy and associated vascular occlusion are a sight threatening manifestation of SLE retinopathy, reported to cause severe visual loss in 55% of patients [26]. The main factor affecting visual outcome in these cases is the occurrence of NV with or without VH, reported in about 40% of the cases [23], as well as an increased risk of developing retinal vein occlusion [27]. Vasoocclusive retinopathy can be the primary manifestation that leads to the diagnosis of SLE [28].

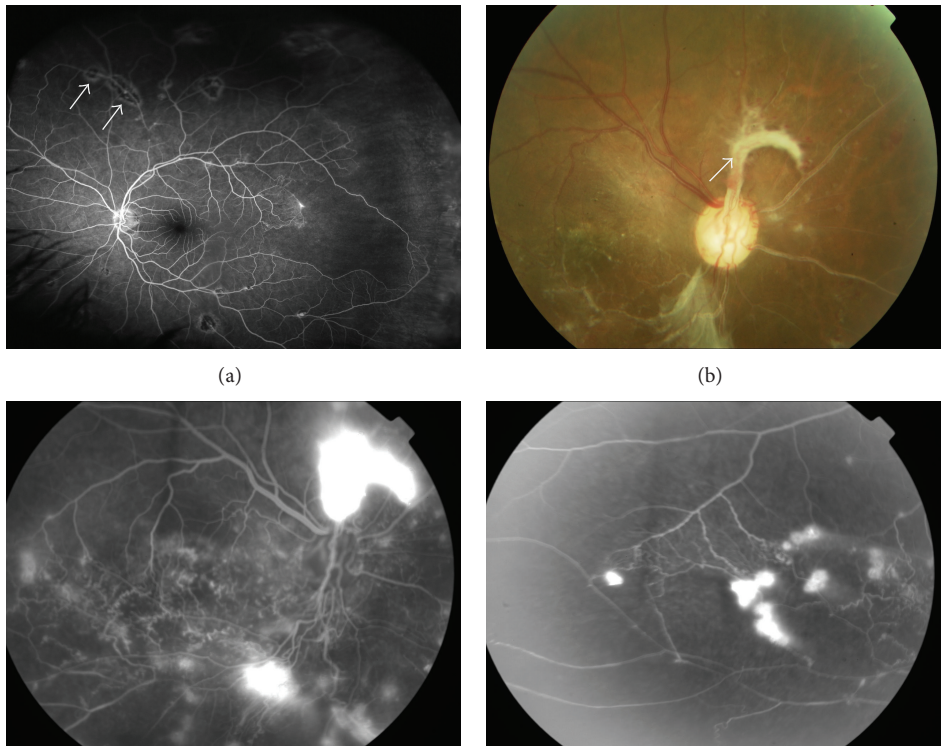
The exact pathogenesis of vascular occlusion is not clear, but there have been proposed theories on the role of immune-complex deposition and complement activation with fibrinoid degeneration of the vascular wall as factors contributing to the vascular damage seen in these cases [29, 30]. Occlusive retinal vasculopathy involving the retinal arterioles may present with cotton-wool spots, predominantly in the posterior pole, representing retinal microinfarctions.

On FFA (Figure 4), vascular occlusion can manifest as widespread arteriolar or branch retinal artery occlusion (BRAO) with severe retinal ischemia and NV [23]. Larger retinal vessels may be occluded leading to retinal and optic disc infarction that may also result in NV [31]. Central retinal artery occlusion (CRAO) and central retinal vein occlusion (CRVO), while very rarely seen in other causes of retinal vasculitis, have been reported secondary to SLE [32–34]. In one report involving 71 patients with SLE and retinal vasculopathy, three (6.3%) of the patients had either CRAO, CRVO, or ischemic optic neuropathy [35].

5. Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of vascular thrombosis, recurrent miscarriage, and antiphospholipid antibodies (IgG anticardiolipin, lupus anticoagulant, and anti-B_2 glycoprotein-I antibody) [36]. Anticardiolipin antibody is associated with a higher incidence of occlusive vasculitis in the eye [37] and was reported to be present in 22.5% of patients with retinal vasoocclusive events in the absence of conventional risk factors of thrombosis [38].

APS can be associated with ocular manifestations, occurring in up to 80% of cases and can commonly result in retinal vasooclusion independent of the presence of SLE (Figure 5) [39]. APS can result in unilateral and bilateral CRVO, CRAO, BRVO, BRAO, and cilioretinal artery occlusion [40–42]. In rare occasions, nonarteritic anterior ischemic optic neuropathy has also been reported [43, 44]. It is not uncommon for patients to initially present with only ocular findings before the diagnosis of APS is established. Therefore, it is reasonable to exclude this condition in younger patients presenting with occlusive vasculitis in the absence of known systemic



(a) (b) (c) (d)

Figure 2: Fundus images of presumed tuberculous occlusive vasculitis. (a) Fundus fluorescein angiography shows peripheral retinal nonperfusion together with small area of hypofluorescence corresponding to chorioretinal lesions along the retinal blood vessels (arrow). (b) A color image showing vascular sheathing together with a fibrovascular tuft originating from the optic disc (arrow), with fluorescein angiography showing (c) leakage at the disc and (d) peripheral capillary dropout and dye leakage from new vessels elsewhere.

risk factors, allowing for early management and preventing further systemic manifestations associated with APS [45].

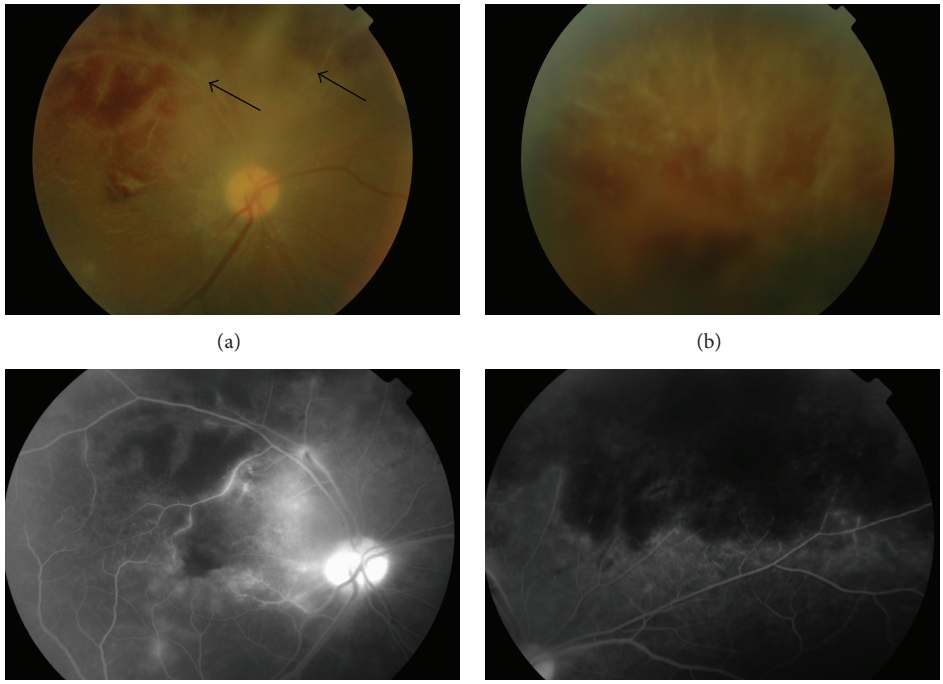
6. Sarcoidosis

Ocular involvement has been observed in 25–60% of patients with systemic sarcoidosis. In these cases, retinal vasculitis in the form of multifocal periphlebitis has been reported in 37% of patients with ocular sarcoidosis [35]. Retinal periphlebitis is a common ocular manifestation and was considered by the first International Workshop On Ocular Sarcoidosis as one of seven clinical signs that comprise the diagnosis of ocular sarcoidosis [46]. Although ocular sarcoidosis is typically associated with nonobstructive vasculitis, ischemic retinal vasculitis has rarely been reported in patients with sarcoidosis. Typical features of the involved vessels include segmental cuffing or extensive sheathing and perivenous exudates, known as "candle wax drippings" associated with vasculitis on FFA that mainly involves midperipheral retinal veins. Additional vascular features include the presence of macroaneurysms, peripheral vessel closure, and NV (Figure 6) [5, 47].

In a study including 75 eyes of patients with sarcoid related uveitis, 37% had retinal vasculitis, three of which had ischemic vasculitis associated with NV [48]. In another study involving 68 patients with posterior uveitis related to sarcoidosis, NVD and VH were reported in 4% of cases, with an increased incidence of VH up to 16% in the young age group [49]. Branch retinal vein occlusion (BRVO), although very rare, has been previously reported especially among young age group in the presence [50] or absence [51] of iridocyclitis. The exact underlying pathology of retinal vasculitis in these cases is not clear. One case report documented the presence of noncaseating granulomas around retinal blood vessels following a postmortem examination of a patient with known idiopathic ischemic retinal vasculitis. Even though such histological finding was suggestive of ocular sarcoidosis, there was no similar findings in the blood vessels elsewhere and no features of systemic sarcoidosis [52].

7. Multiple Sclerosis

The risk of uveitis in patients with multiple sclerosis (MS) is ten times higher compared to the general population, commonly in the form of intermediate uveitis [53]. However, the presence of peripheral periphlebitis was described in the early case reports of MS related uveitis [54, 55]. A review of 1254 uveitis case records at a tertiary eye centre in the United States found 14 (1.3%) to be MS related uveitis, with more than half of the cases associated with vasculitis [56]. Periphlebitis



(a) (b)

(c) (d)

Figure 3: Fundus photographs of branch retinal vein occlusion secondary to Behçet's disease. (a, b) Color images of the right eye showing vascular sheathing (arrows), exudates, and intraretinal hemorrhages. (c) Fluorescein angiography demonstrates multiple areas of hypofluorescence corresponding to areas of retinal hemorrhage and (d) upper retinal quadrant hypoperfusion secondary to vasoocclusion.

(a) (b)

Figure 4: Fundus photographs of SLE associated occlusive retinal vasculitis. (a) Color images demonstrating vascular sheathing (arrows). (b) Fluorescein angiography shows multiple areas of capillary dropout at the retinal midperiphery with leakage from retinal neovascularization (arrows).

has been suggested to be a risk factor for the development of neurological manifestations of MS, including optic neuritis [57, 58].

Many theories have been proposed to explain the pathophysiological correlation between MS and the presence of periphlebitis [59]. In an autopsy series of 93 eyes from patients with an established diagnosis of MS, seven showed segmental perivenular infiltrates of lymphocytes and plasma cells [60]; lymphocyte and plasma cells were also concomitantly observed around retinal and central nervous system veins in two patients with MS, leading to the conclusion that periphlebitis is an early event that may lead to plaque formation in the brain [61].

While periphlebitis has been reported in 20% of eyes [62], occlusive vasculitis and NV (Figure 7) are rare complications in MS related uveitis [63–67]. In a case series of 16 patients with MS related uveitis, eight suffered from ischemic retinal vasculitis with NV requiring SLP, while three eyes had unresolved VH secondary to NV requiring vitrectomy [63]. Peripheral retinal ischemia can be severe and had been

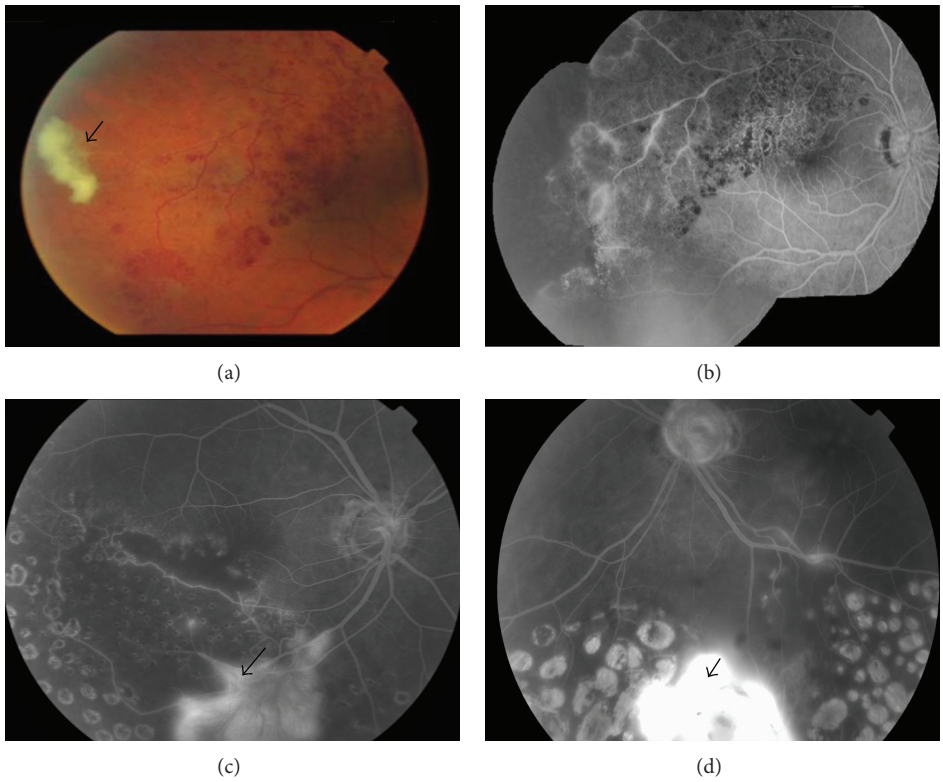


Figure 5: Fundus images show vasooclusion in patients with positive anticardiolipin antibodies. (a) Color image showing peripheral branch retinal vein occlusion with an intraretinal haemorrhage and peripheral fibrovascular tuft (Arrow). (b) Fluorescein angiography of the same patient showing vascular fluorescein leakage together with peripheral retinal nonperfusion. (c, d) Fluorescein angiography of another patient demonstrating bilateral retinal ischemia with areas of hypoperfusion covered with laser photocoagulation scars. There are also bilateral fibrovascular tufts leaking fluorescein (arrows).

reported to cause bilateral rubeosis iridis and neovascular glaucoma. While the rubeotic vessels regressed following treatment with oral corticosteroids and SLP, one eye required trabeculectomy to manage the glaucoma. No steroid sparing drugs were required in this case [68]. Although the presence of VH in uveitis can be highly suspicious of ocular Behçet's or sarcoidosis, the presence of MS may also need to be excluded in patients with intermediate uveitis that develop VH. In a series of 25 patients with MS related intermediate uveitis, six (24%) had periphlebitis associated with retinal ischemia and VH and four had NV on angiography. VH occurred at an average of five years following onset of uveitis, while it was the initial presenting manifestation in two patients [64]. The visual prognosis of MS related uveitis is generally good [56]; however, in those with occlusive vasculitis and NV it may varies. In one report, two of six patients with retinal ischemia and VH had a final vision of 20/80 five years after onset of VH [64].

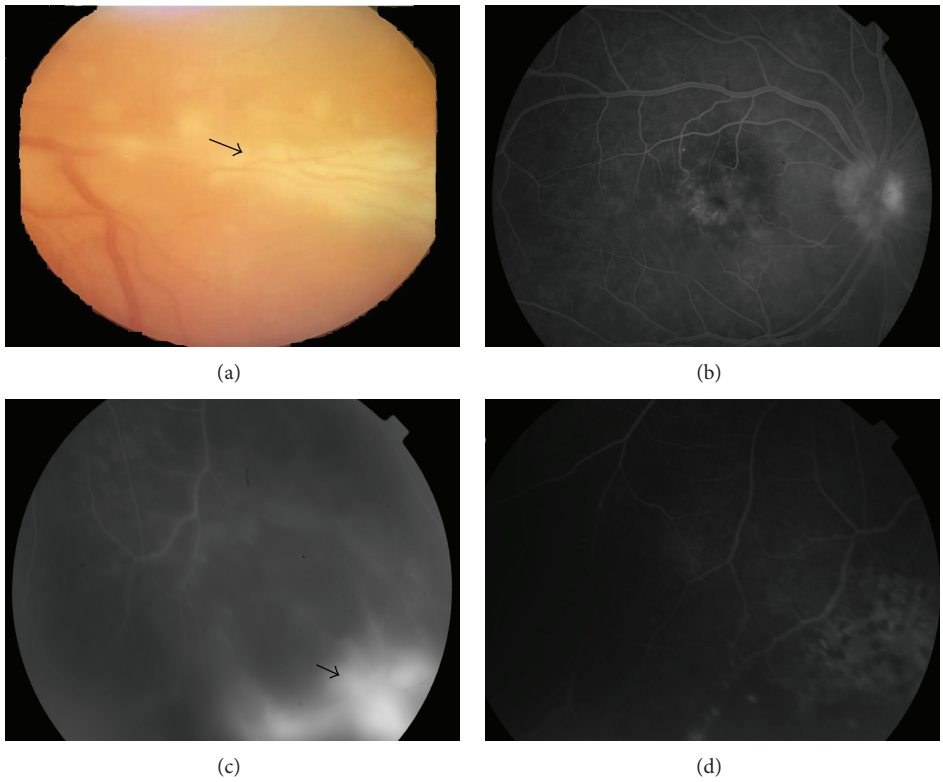
8. Other Causes of Occlusive Retinal Vasculitis

Idiopathic retinal vasculitis, arteriolar macroaneurysms, and neuroretinitis (IRVAN) is characterized by recurrent multiple branch retinal arterial occlusions of unknown cause in one or both eyes of healthy middle-aged patients with no associated ocular or systemic etiology. An important cause of visual loss in IRVAN is chronic macular edema with hard exudate accumulation in the fovea (Figure 8). Vision loss also occurs secondary to peripheral capillary nonperfusion leading to NV and tractional retinal detachment [69].

Crohn's disease has been reported to be associated with ischemic retinal vasculitis, NV [70], neovascular glaucoma [71], and CRAO [72]. West Nile virus infection has been associated with chorioretinitis as its most common ocular finding, whereas occlusive retinal vasculitis is an uncommon finding reported to date in eight cases. Findings include perivascular sheathing, microaneurysms, cotton wool spots, intraretinal hemorrhages, and NV with or without macular ischaemia. Interestingly, six of these cases with established West Nile virus infection also suffered from diabetes mellitus [73, 74].

9. Treatment

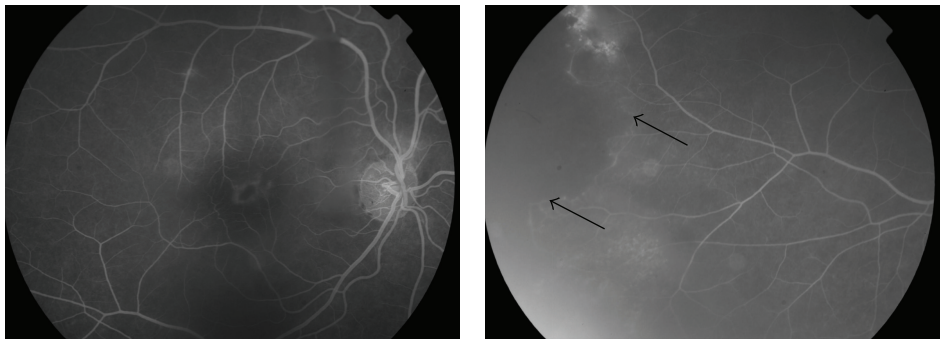
Management of vasculitis and associated vascular occlusion can be challenging as most complications can result in severe visual loss mainly secondary to macular edema, macular ischemia, and retinal detachment.



(a) (b)

(c) (d)

Figure 6: (a) Color fundus imaging of retinal vasculitis secondary to sarcoidosis showing perivenous exudates, "candle wax drippings." (b) Fundus fluorescein angiography of an eye with ischemic vasculitis secondary to sarcoidosis shows leakage at macula secondary to macular edema; (c) peripheral retinal hypoperfusion with focal area of fluorescein leakage corresponding to new vessel formation (arrow). (d) Image taken five months following treatment with systemic corticosteroids and focal laser photocoagulation shows regression of the neovascularization.



(a) (b)

Figure 7: Fundus fluorescein angiography images of a right eye with intermediate uveitis associated with multiple sclerosis; (a) shows fluorescein leakage at the macula secondary to macular edema and (b) peripheral capillary dropout (arrows).

9.1. Systemic Immunosuppressant. Severe retinal vasculitis requires adequate inflammation control using corticosteroids and, in noninfectious vasculitis, may need the addition of IMS agents. BD with severe posterior segment involvement, including retinal vasculitis, is initially treated with a combination of corticosteroids and IMS agents [75]. Cyclosporine A is effective and has long-term inflammatory control but can be associated with renal toxicity [76]. Meanwhile, azathioprine in BD with retinal vasculitis may not be very effective in producing complete resolution and relapse prevention during corticosteroid tapering [77]. In ocular sarcoidosis, the presence of retinal vasculitis requires the use of systemic corticosteroids and often the addition of IMS agents, most commonly methotrexate [78]. In SLE vasculopathy, systemic corticosteroids and IMS, such as cyclophosphamide and mycophenolate mofetil, are established treatments that can

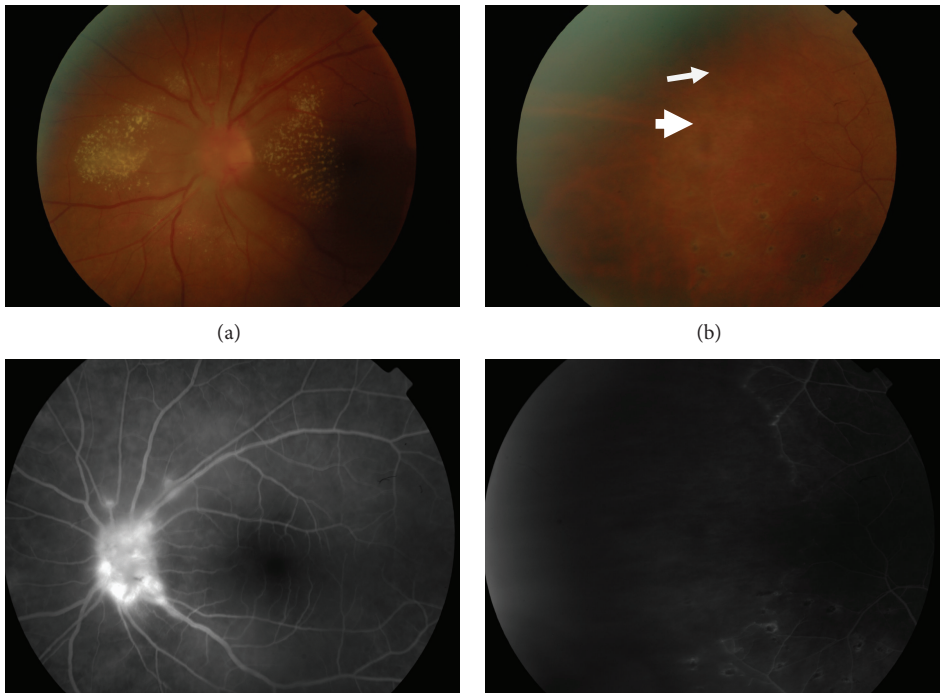


Figure 8: Fundus images of a patient with IRVAN syndrome. (a) Color image showing retinal exudates at the posterior pole involving the macula together with optic disc swelling and hyperemia. (b) Multiple pigmented chorioretinal lesions at the midperiphery (arrow head) together with evidence of vascular sheathing (arrow). (c) Fundus fluorescein angiography showing dye leakage at the optic disc. (d) Wide area of retinal nonperfusion.

reduce vasculopathy and resolve cotton wool spots [79], though there is little evidence supporting their role in preventing the progression of retinal vasooclusion [23]. In presumed TB vasculitis, commencing systemic anti-TB therapy is useful in controlling the inflammation by suppressing the active TB focus, which causes immune activation and triggers uveitis. In addition, adjunctive use of systemic corticosteroid therapy may be required in the management of these cases to prevent damage to ocular tissues especially from delayed hypersensitivity.

9.2. Biologics. Antitumor necrosis factor alpha (TNF-α) drugs such as infliximab and adalimumab have been used successfully in the management of sight threatening retinal vasculitis. In severe ocular BD, anti-TNF-α can be considered as first-line IMS treatment [80] or used in cases refractory to other IMS to reduce the risk of severe visual loss and promote long term remission of uveitis [18, 81, 82]. Extended treatment with infliximab has also been effective in resolving NVD and improving visual outcome in retinal vasculitis secondary to BD [83, 84]. Anti-TNF-α is used successfully in treating refractive cases of sarcoidosis with retinal vasculitis, especially infliximab [85, 86] and adalimumab [87, 88]. Clinical reports on the use of infliximab to control ischemic retinal vasculitis secondary to sarcoidosis have shown good results, especially in cases where ocular symptoms manifest despite the use of IMS agents [89]. Meanwhile, etanercept is not only less effective in managing sarcoidosis but also reported to induce sarcoid intermediate and panuveitis [90, 91]. It should be noted that anti-TNF, often used in the management of severe noninfectious uveitis, should be avoided in treating MS related uveitis as it may precipitate or exacerbate nerve demyelination and worsen the neurological manifestations of this disease [92]. Infliximab used in patients with IRVAN was very successful in inducing dramatic resolution of ocular inflammation, reduction of retinal exudation, improving nerve leakage, and vision improvement after the first dose of infliximab therapy. However, it was not useful in preventing NV formation which occurred months later requiring laser therapy [93].

The use of rituximab, a chimeric monoclonal antibody against CD20+ B-cells, demonstrated some benefit in treating severe cases of SLE in uncontrolled studies but failed to prove superiority against placebo groups in a randomized controlled trial [94]. Rituximab combined with cyclophosphamide infusions was shown to result in rapid resolution of retinal vasooclusion in a pediatric group of SLE patients when used early in the course of the disease [95].

Interferon alfa (INF-α) therapies have been used in selected conditions to control inflammation. In ocular BD, INF-α-2a therapy was reported to provide long lasting remission in up to 55% of cases even after discontinuation of therapy [96]. In a retrospective study, INF-α-2a was effective in controlling retinal vasculitis in 36/38 eyes with BD and in 18/22 eyes with other causes of retinal vasculitis [97]. INF-α-2a may also result in reperfusion of vasooclusion

[98] and induce NVD regression among BD vasculitis even in the absence of concomitant SLP [99]. In a retrospective review, five patients with BD and unilateral ischemic NVD received SLP and three had resolution of NVD following laser treatment while the other two patients responded only following additional treatment with INF-α-2a therapy [21].

The role of INF-β, an established treatment for MS, needs to be further studied to examine its effectiveness in controlling MS with retinal vasculitis. In a small retrospective study of 13 patients with MS related uveitis, ten of which were associated with retinal vasculitis, showed promising results with improvement of visual acuity in 71% of the eyes while a corticosteroid sparing effect was achieved in all cases [100].

9.3. Retinal Laser Photocoagulation and Intravitreal Anti-VEGF Injections. SLP is the main approach in managing NV that form secondary to occlusive vasculitis. In patients with presumed TB vasculitis, SLP was found to be very effective in inducing involution of NV. In a case series of 21 eyes with presumed TB vasculitis that received SLP for NV, there was no recurrence of VH or NV formation within a mean follow-up period of 18 months [12]. In BD, SLP is useful in inducing regression of NV and preventing further complications such as NV glaucoma [101]. In patients with IRVAN, SLP has been recommended in the presence of retinal ischemia before or shortly after the formation of NV regardless of the extent of vascular closure in order to prevent its progression and maintain good visual outcome [102]. Another study suggested using SLP only in eyes with retinal ischemia involving more than two quadrants [103]. In addition to SLP, other treatment options for IRVAN include macular grid laser, vitrectomy, and anti-TNF-α agents with a smaller role for corticosteroids [93, 104].

The primary treatment of retinal NV among patients with SLE and APS vasculopathy involves the use of SLP to the ischemic area with or without intravitreal anti-VEGF agents [40]. Unlike cases with presumed TB vasculitis, SLP is less effective in causing regression of NV in SLE and APS vasculopathy. In a systematic review of the literature, SLP performed on 22 eyes caused regression of the NV and stabilization of vision in only 54% of the cases [23]. Thus, it is not uncommon to see NV formation with subsequent VH and vitreoretinal traction even after retinal laser application [28]. In the absence of randomized clinical trials, it is difficult to assess the role of SLP alone in controlling NV due to the concomitant use of IMS medications in most cases. Intravitreal bevacizumab can be used in eyes with recurrent or persistent NV following SLP. A reported case of SLE with NVE that progressed despite the use of IMS and fill-in laser did respond to one intravitreal injection of bevacizumab resulting in NVE regression with no new bleeding over three months followup [105]. However, bevacizumab itself can reduce retinal perfusion and worsen retinal ischemia and therefore should be administered concomitantly with SLP. In a report of two patients with SLE, one received bevacizumab combined with SLP that resulted in halting the progression of the vascular occlusion with regression of the NVD. The second patient, who did not have laser, had progression of retinal ischemia with secondary NVE within a month of injecting bevacizumab [106]. In rare cases, intravitreal bevacizumab was reported to aggravate capillary nonperfusion within a day following injection despite previous administration of SLP [107].

9.4. Other Treatment Options. Plasma exchange has not shown any additional benefit in the management of nonocular manifestations of SLE and is only recommended for severe SLE crisis such as acute cerebritis or alveolar hemorrhage. However, in severe SLE cases, plasma exchange has been reported to show some benefit in stabilizing occlusive retinal vasculopathy when combined with rituximab infusion [108]. In another case report, plasma exchange combined with methotrexate was useful in providing rapid relief of symptoms but failed to provide a long term therapeutic benefit with a relapse of the vasculopathy six weeks after initiation of plasma exchange [109].

Catastrophic APS is treated using a combination of anticoagulants, corticosteroids, intravenous immunoglobulins, and plasma exchange, followed by prophylaxis with anticoagulant therapy [110]. Recurrence of thrombotic events in patients with APS is common. However, the role of prophylactic long-term anticoagulation therapy in preventing retinal vasoocclusive events is not well established, with a report of consecutive retinal vasooclusion occurring in a patient not on prophylaxis [41]. The role of such prophylaxis treatment in preventing recurrence of retinal vasoocclusive episodes should be addressed in prospective studies.

10. Conclusion

Patients with ischemic retinal vasculitis represent a significant management challenge and if not treated adequately it can lead to severe irreversible visual loss. The use of wide-field angiography should be encouraged in the diagnosis and monitoring of retinal vasculitis as it offers an advantage in detecting peripheral retinal ischemia and NV compared to traditional FFA imaging. Longitudinal or prospective studies are required to assess the effectiveness of IMS therapies in preventing the progression of occlusive retinal vasculitis and its complications.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Role of Autofluorescence in Inflammatory/Infective Diseases of the Retina and Choroid

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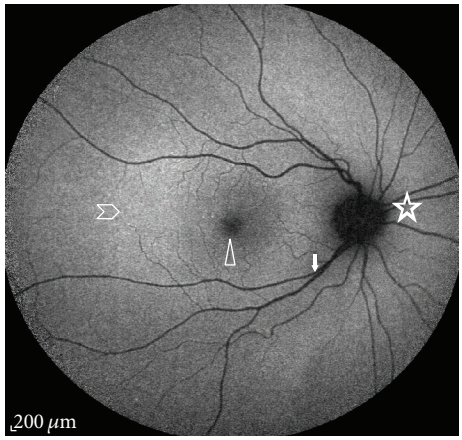
Fundus autofluorescence (FAF) has recently emerged as a novel noninvasive imaging technique that uses the fluorescent properties of innate fluorophores accumulated in the retinal pigment epithelium (RPE) to assess the health and viability of the RPE/photoreceptor complex. Recent case reports suggest FAF as a promising tool for monitoring eyes with posterior uveitis helping to predict final visual outcome. In this paper we review the published literature on FAF in these disorders, specifically patterns in infectious and noninfectious uveitis, and illustrate some of these with short case histories.

1. Introduction

Fundus autofluorescence (FAF) is a noninvasive imaging modality that provides a topographical retinal map of lipofuscin that has accumulated in the retinal pigment epithelium [1]. FAF, first viewed as pseudofluorescence during florescence angiography predye administration [2], has only recently been recognized as a useful indicator for disease activity and extent of retinal pigment epithelium (RPE) damage, assisting an in-depth understanding of the pathophysiologic mechanisms in a wide variety of retinal diseases. As such, it is attracting the attention of many uveitis specialists to investigate its usefulness in various uveitic diseases.

In healthy human retina, the photoreceptor outer segments are shed daily, phagocytosed, and digested by the RPE [3]. Lipofuscin, the dominant fluorophore in the retina, is believed to be the result of accumulation of incompletely degraded products of photoreceptor outer segments in the RPE cytosol [4–6]. Lipofuscin inhibits lysosomal degradation, is photoreactive, and produces oxygen radicals that can lead to a reduced phagocytic capacity of the RPE and eventually RPE cell death and photoreceptor loss [7–12]. Lipofuscins constitute a complex mixture of bisretinoids and contain a broad range of fluorophores with an excitation spectrum ranging from 300 to 600 nm and an emission spectrum from 480 to 800 nm [13]. Retinal photoreceptor degeneration, secondary to retinal disease, can cause visual loss in patients with uveitis. Retinal damage in retinal antigen-induced experimental autoimmune uveitis (EAU), an animal model that resembles some types of human uveitis, has been attributed to blood-borne activated macrophages, which are known to generate various toxic agents [14, 15]. Macrophages and T cells typically infiltrate the retina in the early stages of EAU (days 11-12 after immunization). However, in day 5 after immunization, studies have shown peroxynitrite-mediated nitration of photoreceptor mitochondrial proteins [16], leading to mitochondria dysregulation and cell death [17]. Lipofuscins are thought to represent the breakdown product of various retinal proteins as a result of oxidative damage which is thought to play a role in uveitic diseases [18]. Visualization of lipofuscin accumulation in the RPE reflects disease activity and, in a clinical setting, the intensity of FAF correlates with the amount and distribution of lipofuscin in the RPE layer, serving as a measure of RPE health and function [19]. Therefore, accumulation of lipofuscin in the RPE indicates that oxidative cellular damage has occurred or is occurring [20]. An increase in FAF (hyperautofluorescence) is expected in the presence of increased metabolic activity of



Star: dark optic nerve head
Chevron: parafoveal hyperfluorescence
Arrow head: foveal hypofluorescence
Solid arrow: retinal vessels showing hypofluorescence

Figure 1: Autofluorescence distribution in a normal eye fundus. It is the highest in the posterior pole and gradually diminishes toward the periphery; it also shows hypoautofluorescence over the fovea, the optic nerve head, and retinal vessels.

the RPE, a predictor of dysfunction, and a decrease in FAF (hypoautofluorescence) with the loss of photoreceptors or the RPE [1].

Autofluorescence imaging in normal eyes shows a dark optic nerve head because of the absence of RPE and lipofuscin. Retinal vessels would also appear dark as they block FAF that would otherwise originate from the underlying RPE [13]. The fovea is hypoautofluorescent because of absorption of light by the luteal pigment [21]. The parafoveal region is slightly hyperautofluorescent due to increased RPE and photoreceptor metabolic activity (Figure 1).

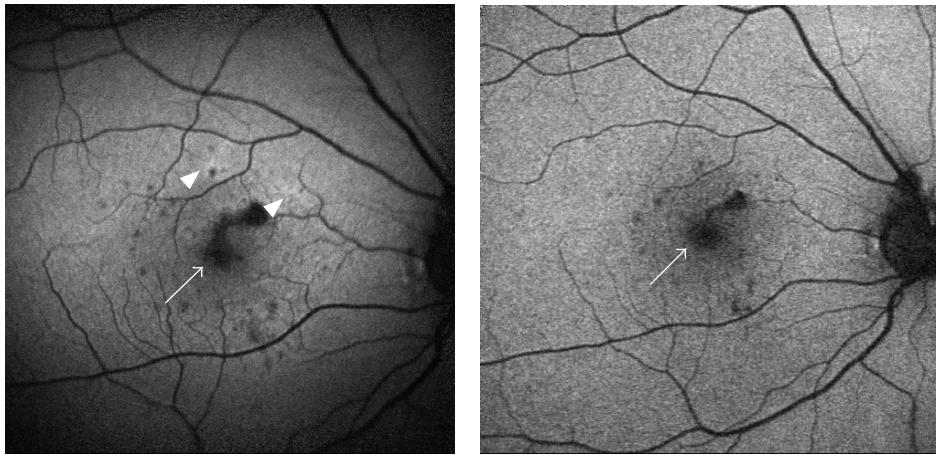
Alterations in FAF have been described in several posterior uveitic syndromes and can help to distinguish between them, provide information on the detection and localization of inflammatory disease activity, and can potentially serve as a prognostic marker for visual outcome. Different autofluorescence patterns are reported in infectious and noninfectious uveitides as well as masquerade syndromes [22]. Most reports share the common finding of hyperautofluorescence with increased disease activity that fades and darkens as the inflammation subsides [23]. In this review we examine FAF patterns in infectious and noninfectious posterior uveitis and discuss the change in these patterns in relation to disease activity.

2. Noninfectious Uveitis

2.1. Multifocal Choroiditis (MFC) and Punctate Inner Choroidopathy (PIC). Punctate inner choroidopathy (PIC) is an uncommon recurrent idiopathic inflammatory disease affecting young myopic women [24], and while both eyes are usually involved this may not occur simultaneously. Clinically, PIC lesions are multiple small yellow-white spots (100–200 μm) with fuzzy borders at the level of the inner choroid and retina. Multifocal choroiditis (MFC) is usually a bilateral condition, which appears as multiple choroidal inflammatory lesions involving the posterior pole and peripheral retina, which may be accompanied by anterior chamber inflammation and vitritis [25]. Symptoms of both conditions usually include photopsias and decreased visual acuity. Choroidal neovascular (CNV) membranes develop in both conditions in up to 76.9% of patients, usually within a year of presentation [26].

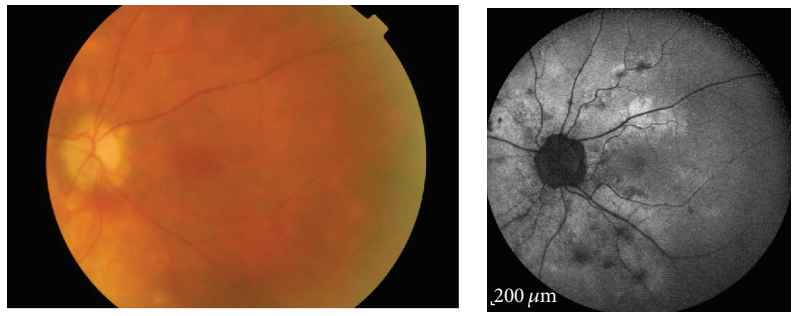
MFC and PIC have a pronounced effect on the morphology and function of the RPE [27]. A recent study conducted on 36 eyes with MFC demonstrated that the number of hypoautofluorescent spots on FAF is far greater than the chorioretinal scars seen on clinical examination. They classified these hypoautofluorescent spots into two patterns according to size [28]. They reported that spots >125 μm were related to visible scars and that those hypoautofluorescent spots <125 μm in diameter were not clinically visible. The smaller spots appeared to cluster around areas of CNV and in some cases appeared to precede the clinically apparent choroidal lesions. The spots seen on FAF are likely to reflect a more accurate measure of disease activity and cellular damage than clinical examination alone, and FAF is less invasive than fluorescein angiography (FA) or indocyanine green angiography (ICG) [29]. A retrospective study of 8 patients with PIC used FAF imaging to assess response of active PIC lesions to immune-modulatory treatment (IMT). Hyperautofluorescence was seen surrounding active PIC lesions and associated CNVs. Hypoautofluorescence occurred when the lesions responded to treatment (Figure 2) and persistence of hyperautofluorescence was associated with a risk of recurrence or continuing active disease. The authors hypothesized that, in the inactive phase of the disease, RPE death results in areas of hypoautofluorescence, although in some instances hypofluorescence at the edges of active lesions may be caused by cellular swelling which could be misleading [30].

2.2. Birdshot Chorioretinopathy. Birdshot chorioretinopathy (BSCR) is a chronic, bilateral posterior uveitis characterized by hypopigmented deep yellow lesions scattered throughout the posterior pole [25, 31, 32]. The disease is more common in middle-aged Caucasians and has a strong correlation with the HLA-A29 antigen [33, 34]. There is widespread consensus that the choroid is the initial site of inflammation due to T-cell accumulation resulting in the distinct BSCR lesions, with a secondary effect on the RPE and photoreceptor layers [35, 36]. Active disease usually presents with mild vitritis, vasculitis, optic disc swelling, and cystoids macular oedema (CME). FAF studies on BSCR patients showed discrete areas of hypoautofluorescence, which did not always correspond to clinically visible birdshot lesions (Figure 3) or were larger and more diffused than any visible lesions [22, 37]. A 17% incidence of linear perivascular hypoautofluorescence that correlates with clinical findings has also been reported [38]. These studies identified that about 80% of eyes with BSCR had more numerous and more easily recognized abnormalities on FAF than on fundus photography, with similar findings documented with the more invasive ICG angiography [38].



(a) (b)

Figure 2: Fundus autofluorescence (FAF) images of a young female with punctate inner choroiditis. (a) FAF shows hyperautofluorescence halos (arrow heads) and multiple hypoautofluorescent spots (arrow). The spots are surrounded by a hyperautofluorescent halo, denoting continued cellular damage and ongoing active inflammation. (b) FAF captured 5 months after immunosuppression was started shows diminished hyperautofluorescence and less hypoautofluorescent spots.



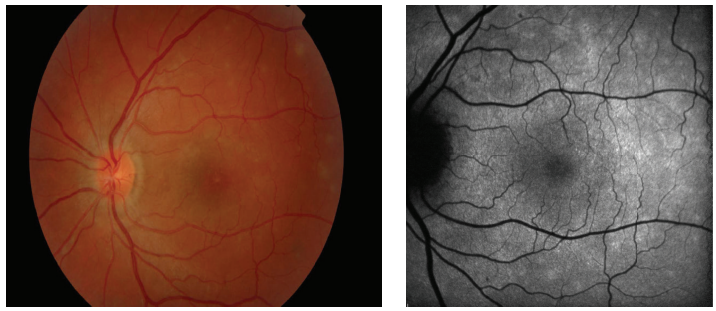
(a) (b)

Figure 3: Areas of hypoautofluorescence in birdshot chorioretinopathy. (a) corresponds to the typical lesions in most parts and (b) shows more widespread lesions than the ophthalmologically visible area of involvement.

Hypoautofluorescent lesions were better correlated with visible BSCR lesions in eyes with advanced disease [22]. Patients with predominantly choroidal inflammation without overlying RPE damage have fewer FAF findings, with prolonged choroidal inflammation resulting in eventual RPE damage and subsequent photoreceptor loss, related to vision and visual field changes in these patients. Patients with chorioretinitis, including a BSCR patient, demonstrated that visual field changes correlated with areas of reduced FAF in both eyes [39]. In BSCR patients with placoid areas of hypofluorescence in the macula, there was a poorer visual outcome and thinner macula on optical coherence tomography (OCT) than patients with no macular involvement [38]. These observations serve to support the argument of initiating immunosuppressive therapy in patients with BSCR lesions before the onset of RPE damage, as evidenced by the appearance of overlying hypoautofluorescent areas [31].

2.3. Multiple Evanescent White Dot Syndrome. Multiple evanescent white dot syndrome (MEWDS) is a retinochoroiditis that is typically described in young myopic females and is occasionally preceded by a viral prodrome. Classically, patients complain of sudden visual loss in the form of central or paracentral scotomas or enlarged blind spot. Fundus examination typically reveals multiple small yellow-white spots in the posterior pole of various sizes ranging from 100 μm to 200 μm, as well as fine orange granularities or specks at the fovea [40–42]. OCT performed on the affected areas during the acute phase reveals hyperreflective lesions in the subretinal space and multifocal attenuation and disruption of the photoreceptor inner/outer segment (IS/OS) junction [43, 44]. In one study a strong correlation was noted between hypofluorescent pots on ICG and disruption of the IS/OS junction on OCT, supporting the hypothesis that the disease initially starts in the photoreceptor layer and not in the choroid [43]. The disease has a favourable prognosis and is usually self-limiting, with full recovery of vision within weeks to months.

During the acute phase of the disease, FAF demonstrates multiple ill-defined spots of hyperautofluorescence



(a) (b)

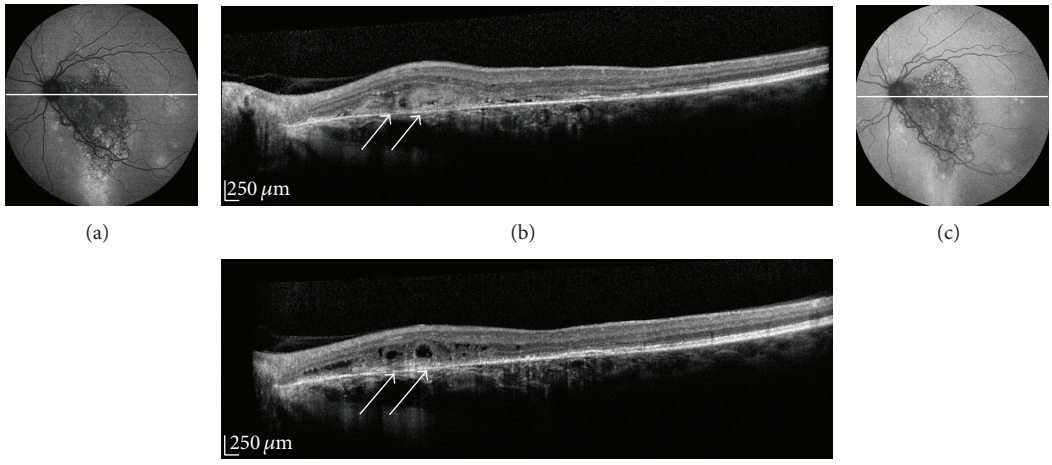
Figure 4: Areas of hyperautofluorescence in multiple evanescent white dot syndrome. (a) Colour fundus images showing multiple small yellow-white spots and fine orange granularities at the fovea. (b) FAF of the same eye showing multiple ill-defined spots of hyperautofluorescence.

in correspondence with the clinically visible white spots (Figure 4), which also correspond to the lesions seen on FA. This hyperautofluorescence pattern may be secondary to disrupted or misaligned photoreceptors or to an increased rate of shedding of the photoreceptor outer segments that are related to active inflammation. Following resolution of the inflammation, the hyperautofluorescent lesions disappear [45].

2.4. Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE). Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an idiopathic bilateral condition typically affecting healthy young adults and characterized by rapid loss of central vision with multiple round, placoid, and gray-white lesions at the level of the RPE [46]. It presents with a distinct FAF pattern of hypoautofluorescence during the acute phase, related to a masking effect secondary to overlying oedematous retinal cells. As the lesions and oedema resolve, a hyperautofluorescence pattern emerges due to photoreceptor loss and release of lipofuscin and other fluorophores [47].

2.5. Primary Intraocular Lymphoma (Primary Vitreoretinal Lymphoma). Primary ocular non-Hodgkin's lymphoma, commonly referred to as primary intraocular lymphoma (PIOL) [48] or recently suggested to be renamed primary vitreoretinal lymphoma (PVRL), is a subset of primary central nervous system lymphoma (PCNSL). It is an aggressive neoplasm, most frequently of B-lymphoid cell origin and rarely of T-lymphoid cell origin [49]. It may take up to 24 months for the diagnosis of PVRL to be established with a median survival period of 31 months [50–52]. Eighty percent of patients with PVRL will eventually develop CNS lymphoma while 20% of PCNSL cases will develop ocular involvement [53]. Typically, patients present in the 5th to 7th decade with a masquerade syndrome of a chronic intermediate uveitis [54, 55]. Imaging of the eye and brain is the first step in evaluating these patients. However, patterns of FAF in eyes with PVRL may be variable and confusing. Several studies compared the sensitivity and predictive values of FA, spectral-domain OCT (SD-OCT), and FAF images in eyes with known PVRL [56, 57]. They found that a granular autofluorescence pattern could be seen in majority of eyes with active disease. Furthermore, this granular FAF pattern was also observed in some eyes where the classic leopard spot pattern on FA was not clear or when FA could not be performed. Hyperautofluorescent spots appeared to correlate with the hypofluorescent spots on FA and the nodular hyperreflective spots on OCT (Figure 5), all of which were suggestive of active disease. Hyperautofluorescence on FAF is thought to indicate RPE involvement by the lymphomatous infiltrates in the sub-RPE space. It is also possible that the hyperautofluorescence pattern seen is the result of lipofuscin accumulation in the RPE cells adjacent to the tumour [56]. Hypoautofluorescence areas may be caused by blockage of autofluorescence by the infiltrating tumour cells or RPE atrophy which can result from tumour resolution [57]. Hence, abnormal autofluorescence can be helpful in raising the possibility of lymphoma or recurrence in a patient with known PVRL. Since PVRL is a potentially fatal malignancy, early and accurate diagnosis is crucial.

2.6. Vogt-Koyanagi-Harada (VKH) Disease. Vogt-Koyanagi-Harada (VKH) disease is a bilateral granulomatous panuveitis associated with an autoimmune reaction against melanocytes and associated with multisystemic involvement [58, 59]. During the acute phase of the disease patients can present with bilateral panuveitis and exudative retinal detachments [58, 60, 61]. It is believed that these detachments and the pinpoint leakage on FA are the result of granulomas in the choroid causing alterations in the RPE and patients should be treated promptly to prevent permanent ocular damage and visual loss. Some patients continue to progress and develop chronic disease with choroidal depigmentation and RPE clumping, resulting in a sunset glow fundus [58, 60]. Koizumi et al. examined the FAF images of 10 eyes from five patients with acute VKH. These patients were followed for up to 6 months and analyzed retrospectively [62]. They classified FAF findings into two distinct patterns; the first was described in acute patients who received early intensive immunosuppression and showed mild hyperautofluorescence, which diminished in size and intensity during followup and returned to normal upon disease remission. The second pattern was seen in patients who either were not treated or in whom treatment



(a) (b) (c)

(d)

Figure 5: Fundus autofluorescence (FAF) images of a male with primary vitreoretinal lymphoma (PVRL). (a) FAF images of a patient with PVRL showing predominantly hyperautofluorescence in the form of granular hyper- and hypoautofluorescence, (b) OCT scan showing areas of nodular hyperreflective spots at the level of the RPE (arrows). (c) 2 years following the treatment the FAF image shows less marked granular hyperautofluorescence, as well as a fading of the nodular RPE hyperreflective spots previously noted on OCT ((d), arrows).

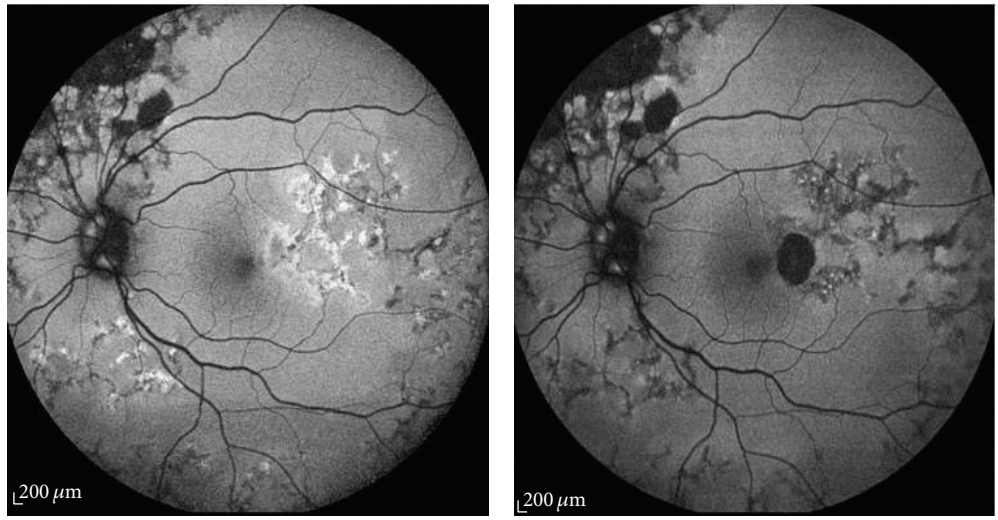
was delayed. These showed scattered and widespread areas of hyperautofluorescence, which corresponded to areas of ICG hypofluorescence. This pattern resolved within 6 months to leave an intermingled pattern of hyper- and hypoautofluorescent spots throughout the retina. In a separate case report, a target-like pattern of hyper- and hypoautofluorescence areas was noted, reflecting changes attributed to the presence of serous retinal detachment [63]. During the chronic phase of the disease FAF is generally normal as sunset glow fundus is not related to RPE loss, but rather to postinflammatory depigmentation or loss of choroidal melanocytes [64, 65]. Thus FAF may assist in identifying the acute phase of VKH and disease remission.

3. Infectious Uveitis

3.1. Serpiginous-Like Choroiditis (SLC). Serpiginous choroiditis is a chronic, progressive, recurrent inflammatory disease affecting primarily the inner choroid and RPE [66]. Conversely, serpiginous-like choroiditis of presumed tubercular etiology (SLC) [67, 68] is a distinct clinical entity that begins with multifocal choroidal lesions that coalesce and progress in a serpiginoid pattern at the posterior pole of the eye [68, 69]. SLC manifests as multifocal placoid lesions that advance in a serpiginoid fashion and become confluent. The diagnosis is supported by a positive interferon-γ release assay or PPD skin test, absence of other known causes of infectious and noninfectious uveitis, and a response to antituberculosis therapy [70, 71]. The choriocapillaris has been shown to be the most affected layer in serpiginous choroiditis (SC) and most likely in SLC [72]. In a prospective study on four eyes in 3 patients with SLC changes in high-resolution SD-OCT scans were compared with FAF scans [73]. During the acute stage, there was an ill-defined area of hyperautofluorescence around the lesion. The SD-OCT passing through this area showed a localized, indistinct area of hyperreflectivity in the outer retinal layers involving the RPE and there was no increased backscatter from the inner choroid. As the lesions began resolving, they became well defined and acquired a thin border of hypoautofluorescence though remaining predominantly hyperautofluorescent centrally. The SD-OCT scan through the hyperautofluorescent area showed disappearance of the hyperreflectivity in distinct areas that were replaced by irregular, hyperreflective lumpy elevations of the outer retinal layers. At this stage, there was increased reflectance from the choroidal layers due to the attenuating RPE-photoreceptor complex. As the lesions healed further, they appeared stippled with predominant hypoautofluorescence. The SD-OCT scan showed loss of RPE, IS/OS junction, while the increased reflectance from the choroid persisted. In this study all eyes with active lesions of SLC illustrated progressive changes in the outer retinal layers on OCT scans that correlated with the FAF changes. The FAF images demonstrated the transition from initial hyperautofluorescence seen in the acute lesions to predominant hyperautofluorescence in the healed stage (Figure 6). The FAF signals were regarded as a strong indicator to the status/health of RPE cells.

In another prospective consecutive case series of twelve patients with SC or SLC, all underwent serial FAF imaging [74]. Hypoautofluorescent halos surrounding the edges of hyperautofluorescent lesions were seen and correlated with active inflammation as assessed by FA.

Transitional SC is an intermediate stage between active and inactive inflammation. FA indicates that most or all of the inflammation has subsided. FAF images show a hypoautofluorescent line that surrounds all edges of the hyperautofluorescent lesions indicating that the SC lesions are stable and subsequently they do not increase in size. Inactive lesions are characterised by FAF images that are dark with very sharp borders due to complete loss of fluorophores. There is no hyperautofluorescence at the edge and this pattern correlates with inactive inflammation in FA and lesions that



(a) (b)

Figure 6: Fundus autofluorescence image of left eye of a male patient with tuberculous choroiditis. (a) An ill-defined halo of hyperautofluorescence corresponding to the active lesion, giving it a diffuse, amorphous appearance. (b) Two months later, a thin rim of hypoautofluorescence appears surrounding the predominantly hyperautofluorescent lesion.

are clinically stable and in remission. These findings led to a paper in which SLC was differentiated from SC based on the FAF image findings. In this study FAF images of SLC lesions demonstrated a variegated pattern of hypo- and hyperautofluorescence signals that were distinct from the homogenous, contiguous hypoautofluorescence typically seen in SC [22, 75].

In these situations, FAF has proved to be a useful and easy to use clinical tool that can be employed to evaluate the extent of the affected area. FAF highlights subtle activity within the lesions, which can otherwise be easily missed. It is suggested that it can be used with caution to differentiate SC from SLC; however further studies are warranted. FA continues to be the gold standard imaging technique in cases where CNV is suspected and OCT remains very useful for monitoring disease activity.

3.2. Other Infectious Conditions. The use of FAF in the management of infectious uveitis has only been sporadically evaluated, with few reports regarding fluorescence patterns in different conditions. In patients with ocular syphilis, a hyperautofluorescence pattern, overlying the retinal lesion, has been described. As systemic antibiotic treatment is initiated this pattern resolves with a return to a normal autofluorescence pattern upon disease remission [76]. In a single case report of an immunocompromised patient who developed progressive outer retinal necrosis, secondary to varicella zoster virus, a stippled hyperautofluorescence pattern within extensive zones of hypoautofluorescence was noted, which corresponded to widespread RPE and outer retinal damage [77]. In patients with active cytomegalovirus retinitis a hyperautofluorescent area, corresponding to the advancing border of active retinitis, has been observed. However, later scans revealed a varied pattern of FAF, limiting its usefulness in monitoring disease progression and resolution [78].

4. Conclusion

Generally, in posterior uveitides, hyperautofluorescence indicates disease activity while quiescent disease and areas of chorioretinal atrophy or scarring are hypoautofluorescent. Fundus autofluorescence has recently been recognized as a useful noninvasive modality that is accurate in detecting early disease activity and extent of RPE damage. It serves in understanding pathophysiologic mechanisms and proves to be a valuable prognostic indicator in many posterior uveitides. Interestingly, in some conditions such as PIC, SLC, PVRL, MEWDS, and BSCR, FAF imaging reveals more widespread areas of disease activity than can be seen clinically. Autofluorescence is an adjunctive and helpful noninvasive tool in conjunction with other imaging modalities such as OCT, FFA, and ICG.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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