Survey of Ophthalmology 70 (2025) 451–466

Contents lists available at ScienceDirect

Survey of Ophthalmology

journal homepage: www.elsevier.com/locate/survophthal

Review article

Inflammatory choroidal neovascularization: An evidence-based update

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ARTICLE INFO

Keywords:
Inflammatory choroidal neovascularization
Intravitreal anti-VEGF
Posterior uveitis treatment
Non-infectious uveitis
Infectious uveitis

ABSTRACT

Inflammatory choroidal neovascularization (iCNV) significantly contributes to vision impairment and ranks as the third primary cause of CNV. Arising from both infectious and noninfectious uveitis, iCNV's pathogenesis involves Bruch membrane rupture, local inflammation, and choriocapillaris ischemia. The diagnosis of iCNV is challenging due to its symptomatic overlap with other uveitis-related conditions. We emphasize the importance of advanced multimodal imaging techniques, particularly optical coherence tomography (OCT) and OCT angiography (OCTA), for early detection and differentiation of iCNV from other types of CNV. Although anti-vascular endothelial growth factor agents have shown high efficacy in treatment, the integration of these treatments with anti-inflammatory therapies remains a critical area of active research. The diversity of uveitis presentations and the rarity of iCNV have resulted in a scarcity of randomized clinical trials, leading to reliance on fragmented data from case reports and series. We consolidate the most recent studies to provide a comprehensive, updated overview of the epidemiology, risk factors, pathogenesis, imaging techniques, and treatment modalities for iCNV, aiming to support clinical decision-making. The absence of standardized guidelines highlights the need for further research to establish best practices for managing iCNV effectively.

1. Introduction

Inflammatory choroidal neovascularization (iCNV) stands as a significant cause of vision impairment, ranking as the third most prevalent type of CNV after age-related macular degeneration (AMD) and pathologic myopia (PM).[64] Manifesting in both infectious and noninfectious uveitis, iCNV notably exacerbates vision loss in these patients.[2] As the incidence of uveitis has increased globally—propelled by factors such as globalization and migration—the burden of iCNV correspondingly increased. This uptick has spotlighted previously underrecognized infectious agents and revealed shifts in noninfectious uveitis patterns due to genetic diversities introduced by migration.[62] This progress has stimulated numerous studies aimed at refining iCNV management strategies.[8]

Diagnosing iCNV poses significant challenges, necessitating differentiation from other ocular inflammation features like choroiditis, chorioretinal scarring, and other inflammatory lesions.[8] Moreover, distinguishing iCNV from other forms of CNV, especially those secondary to PM, is complex owing to overlapping risk factors.[24] Advances in imaging, especially with high-resolution optical coherence tomography (OCT) and OCT angiography (OCTA), have improved our understanding and diagnostic capabilities. The treatment landscape for iCNV has also evolved with the introduction of new-generation, multi-target anti-vascular endothelial growth factor (anti-VEGF) agents, which may potentially improve clinical outcomes.[12]

Despite these advancements, the exact pathogenesis of iCNV and optimal treatment strategies, including adjunctive therapies to address underlying inflammation, have yet to be established. The rarity and heterogeneity of this condition challenge robust data accumulation, resulting in a scarcity of randomized clinical trials and often leaving clinicians without clear guidance on accurate diagnosis and effective treatment planning. This review synthesizes the most recent studies to provide a practical clinical perspective on the epidemiology, risk factors, pathogenesis, diagnostic and therapeutic advancements of iCNV.

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https://doi.org/10.1016/j.survophthal.2024.12.004
Received 23 August 2024; Received in revised form 14 December 2024; Accepted 16 December 2024
Available online 18 December 2024

2. Methods

We conducted a literature review using PubMed for articles published from 1979 to 2024. The search employed the keywords "inflammatory choroidal neovascularization," "intravitreal anti-VEGF," "posterior uveitis treatment," "non-infectious uveitis," and "infectious uveitis." This search aimed to identify relevant studies on iCNV, focusing on pathogenesis, risk factors, epidemiology, multimodal imaging, and treatment approaches.

Inclusion criteria were studies written in English that provided insights into the aforementioned topics, excluding any that reported on imaging techniques or treatments that are considered obsolete or are no longer used in clinical practice. Predominantly, studies with sample sizes greater than 4 were considered; however, studies with smaller sample sizes were included if they addressed rare diseases where larger studies were unavailable.

All imaging figures in this article were sourced from the Department of Ophthalmology at the IRCCS San Raffaele Hospital, Milan, Italy. The imaging modalities included infrared reflectance, blue autofluorescence (AF), spectral-domain OCT, fluorescein angiography (FA), and indocyanine green angiography (ICGA). These were performed using the HRA2 + OCT Spectralis (Heidelberg Engineering, Heidelberg, Germany). Additionally, swept-source OCTA was conducted using the PLEXElite 9000 system (Carl Zeiss Meditec Inc., Dublin, CA, USA); ultra-widefield color retinography, green AF, FA, and ICGA utilized the Optos Silverstone (Optos PLC, Dunfermline, UK).

3. Epidemiology

iCNV arises from both infectious and noninfectious uveitis. Data on non-infectious uveitis are substantially more robust, whereas insights into iCNV related to infectious diseases remain limited, primarily consisting of case series and individual reports.[2,10]

3.1. Noninfectious uveitis

The most comprehensive study on noninfectious uveitis by Baxter et al. analyzed 15,137 eyes in a retrospective cohort of patients observed from 1978 to 2007 at five academic ocular inflammation centers in the United States. Patients with known HIV infection were excluded. The study revealed that iCNV primarily occurs in cases of posterior uveitis and panuveitis, with prevalences of 2 % and incidences of 2.7 % within 2 years, respectively. Conversely, iCNV associated with intermediate uveitis is relatively rare. The predominant etiologies identified included punctate inner choroidopathy/idiopathic multifocal choroiditis (PIC/iMFC), Vogt-Koyanagi-Harada (VKH) syndrome-possibly less common in the Western world due to earlier diagnosis- and occasional cases with serpiginous choroiditis (SC) syndrome (Fig.s 1–3).[10]

Supporting these findings, a study by Woronkowicz and coworkers that included 204 eyes from a UK uveitis referral hospital found that 85.3 % of iCNV cases were related to PIC/iMFC, underscoring the high incidence of iCNV in these conditions, as also reflected in smaller case series.[88] Other entities within the spectrum of white dot syndromes, such as acute posterior multifocal placoid pigment epitheliopathy

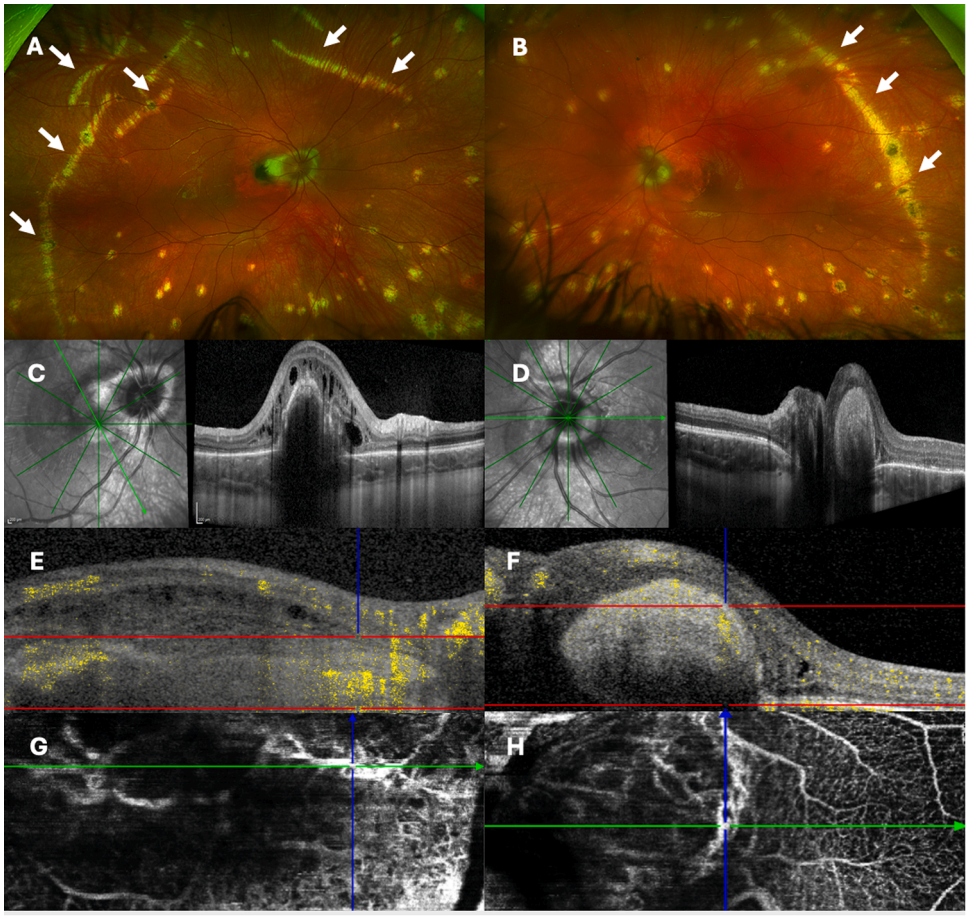

Fig. 1. Multimodal imaging of bilateral peripapillary iCNV in a patient with punctate inner choroidopathy/idiopathic multifocal choroiditis (PIC/iMFC). This figure presents ultra-widefield pseudocolor fundus photographs (A, B) depicting multiple yellowish round lesions in the retinal periphery, accompanied by Schlaegel lines (arrows) and a yellowish peripapillary lesion in both eyes. OCT (C, D) reveals subretinal hyperreflective material, retinal thickening, and cystoid macular edema. OCT angiography (E, F, G, H) highlights a vascular network consistent with iCNV.

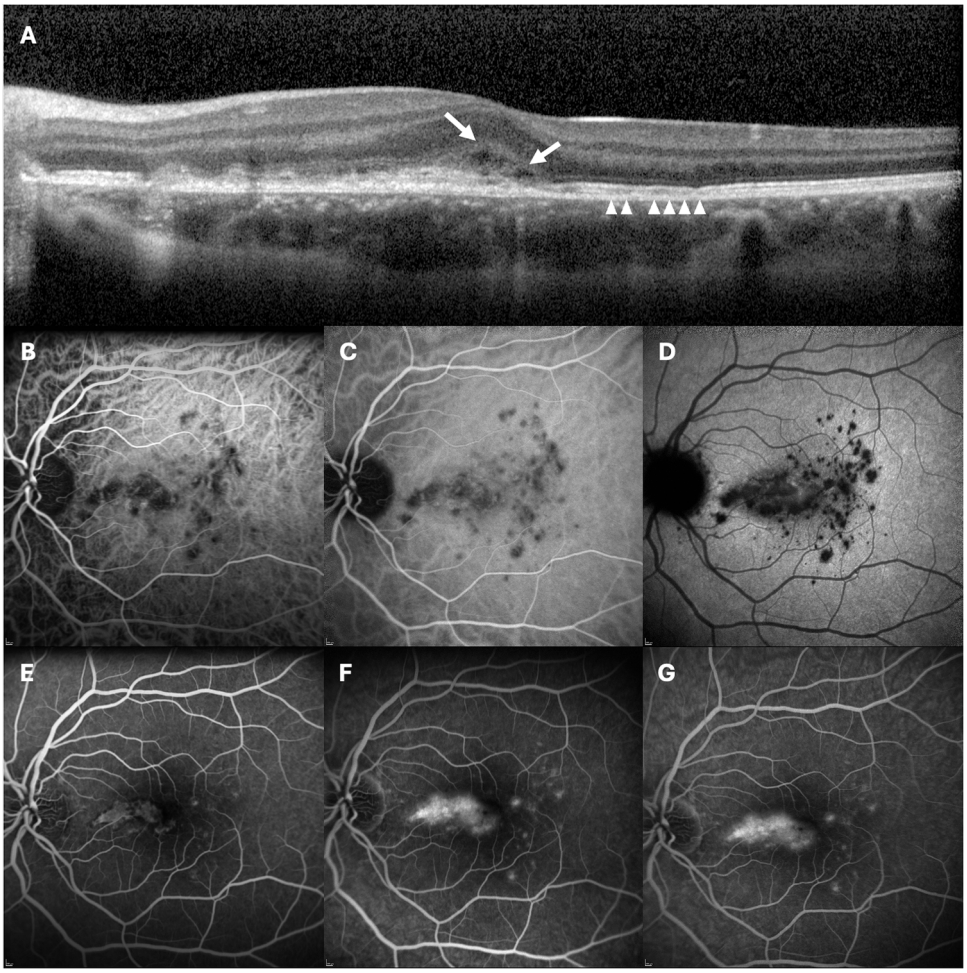

Fig. 2. Multimodal imaging of iCNV in a patient with punctate inner choroidopathy/idiopathic multifocal choroiditis (PIC/iMFC). OCT (A) captures subretinal hyperreflective material along with subretinal fluid cysts (arrows). There is hyperreflective splitting of the Bruch's membrane/retinal pigment epithelium complex, typical of PIC/iMFC, with hyperreflective material with fuzzy margins infiltrating the outer retina. The image displays areas of ellipsoid zone rarefaction (arrowheads), consistent with photoreceptor/RPE dysfunction. Early-phase indocyanine green angiography (ICGA) (B) exhibits marked hypofluorescence and faint hypofluorescence, intensifying through the intermediate (C) and late phases (D). This angiographic behavior is consistent with active choroiditis due to PIC/iMFC; however, faint hypofluorescent spots that become larger and more visible in the late stages, corresponding to ellipsoid zone rarefaction, are compatible with secondary multiple evanescent white dot syndrome (MEWDS), associated with active choroiditis. Fluorescein angiography displays initial hyperfluorescence (E), followed by progressive leakage and pooling in the intermediate (F) and late (G) phases.

(APMPEE) and acute zonal occult outer retinopathy (AZOOR), and the newly described multizonal outer retinopathy and retinal pigment epitheliopathy (MORR), are less commonly linked to iCNV (Fig. 4).[20,38,74] Additionally, stromal choroiditis conditions, including sympathetic ophthalmia (SO), birdshot chorioretinopathy (BSCR), and sarcoidosis, have been also associated with iCNV.[28,40,41,54]

A few case reports have highlighted iCNV as a manifestation of vitreoretinal lymphoma (VRL), which is part of the uveitis masquerade syndromes, often presenting with vitritis and intraretinal or subretinal/sub- retinal pigment epithelial (RPE) infiltrates (Fig. 5). This suggests that VRL should be considered in cases of iCNV where the etiology remains unclear.[44,75]

3.2. *Infectious uveitis*

The primary agents implicated in the infectious causes of iCNV include histoplasmosis (including series reporting its presumed infection), toxoplasmosis, tuberculosis, and toxocariasis (Fig. 6).[2] There are also less frequent instances of syphilis, congenital rubella, and West Nile virus (Fig. 7).[2] Notably, histoplasmosis exhibits a higher prevalence in American and European populations, while toxoplasmosis is more prevalent in South Asia, highlighting the significant role of geographic factors in the distribution of infectious iCNV.[2,21,78]

There have been documented cases of iCNV associated with acute idiopathic maculopathy, which is plausibly triggered by a Coxsackie virus infection.[76,91] Lastly, rare occurrences of endogenous endophthalmitis linked with iCNV further expand the spectrum of infectious contributors to this condition (Fig. 8).[39]

4. Risk factors and pathogenesis of iCNV

The pathogenic mechanisms underlying iCNV are multifaceted and continuously evolving with ongoing research. These mechanisms include mechanical damage, inflammation, ischemia, and potentially genetic predisposition, collectively shaping the complex nature of iCNV (Fig. 9).

4.1. *Genetic and systemic influences*

Genetic factors might eventually contribute to the development of iCNV, as suggested by the observed higher incidence in cases of bilateral uveitis. The occurrence of iCNV in one eye, in fact, significantly increases the likelihood of iCNV in the other eye, suggesting systemic factors (e.g, genetic) may exacerbate the condition in patients with

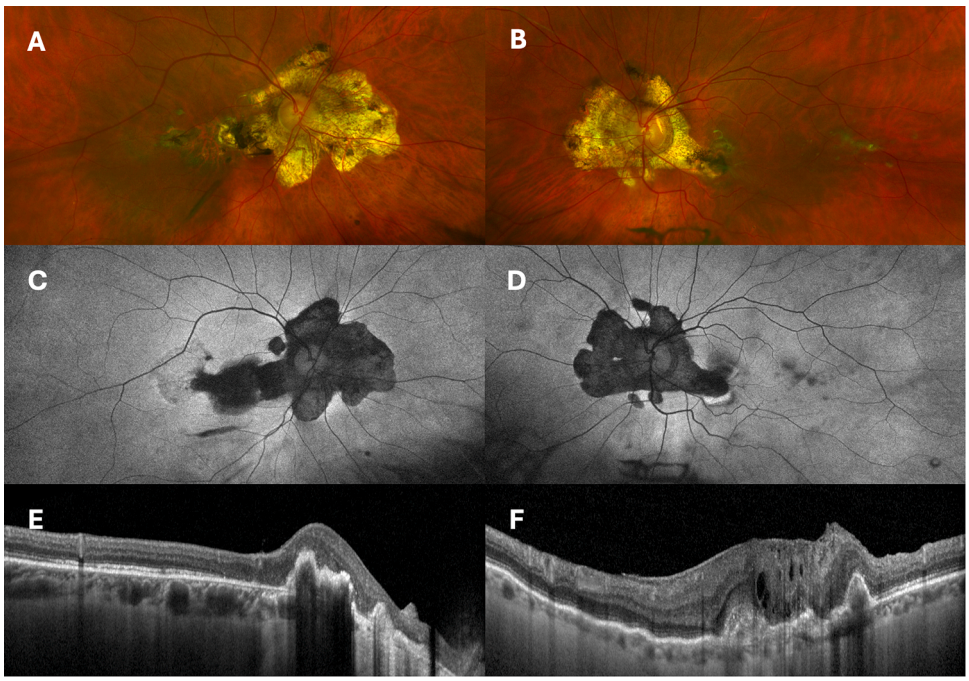

Fig. 3. Multimodal imaging of bilateral iCNV in a patient with serpiginous choroiditis. Ultra-widefield pseudocolor fundus photographs (A, B) display parapapillary chorioretinal atrophy, appearing as hypoautofluorescent areas on fundus autofluorescence (C, D). OCT (E, F) reveals fibrovascular RPE detachment consistent with iCNV, accompanied by outer retinal atrophy in the right eye and intraretinal fluid and fuzzy hyperreflective subretinal material in the left eye.

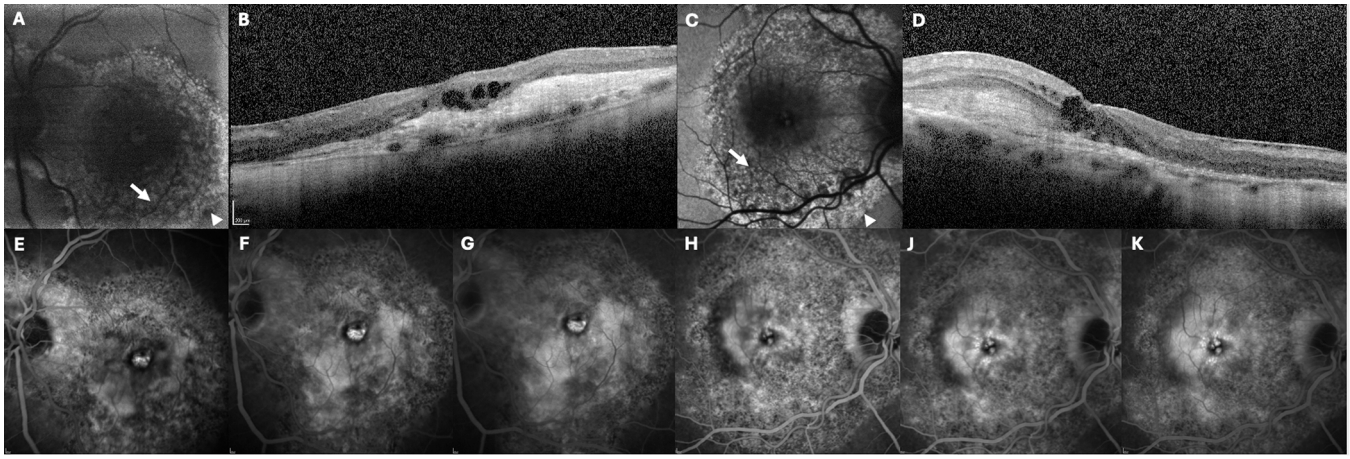

Fig. 4. Multimodal imaging of bilateral iCNV in a patient with multizonal outer retinopathy and retinal pigment epitheliopathy. Blue-light autofluorescence (A, C) reveals a posterior-pole lesion featuring a hypoautofluorescent core encircled by a speckled hypo-hyperautofluorescent ring (arrows) and a distinct hyperautofluorescent border (arrowheads). OCT (B, D) illustrates a thick fibrovascular retinal pigment epithelium detachment and intraretinal fluid. Fluorescein angiography displays early (E, H) hyperfluorescence due to a window defect, progressing to leakage in later phases of the examination (F, G, J, K).

systemic uveitis.[10]

4.2. Uncontrolled inflammation

Inflammation is a primary acquired risk factor for iCNV. Eyes with active or inadequately treated inflammation are particularly vulnerable.[66] Studies have shown that eyes graded 2 + or higher in anterior chamber cell evaluations have a significantly increased risk of developing iCNV within 2 years, as demonstrated in a retrospective longitudinal cohort study across five US centers.[10] iCNV has also been associated with preretinal neovascularization, likely due to shared pathological processes such as ischemia and inflammation-driven VEGF production.[69]

In a broader context, cytokines such as tumor necrosis factor α (TNFα) and IL-1 recruit macrophages that contribute to the inflammatory component of iCNV.[51] Other cytokines, like IL-2, IL-6, and IL-10, may induce the secretion of matrix metalloproteinases that activate VEGF-165 and degrade the extracellular matrix, thereby facilitating neovascularization.[27] Chronic inflammation may directly impair perfusion, creating a retinal-choroidal hypoxia gradient that fosters iCNV. Hypoxia further stimulates cytokine production via hypoxia-inducible factor (HIF) pathways, highlighting the interplay between inflammation and ischemic processes.[23]

4.3. Choriocapillaris ischemia

iCNV can develop without overt signs of active uveitis, potentially due to low-grade, subclinical inflammation affecting the choroid and

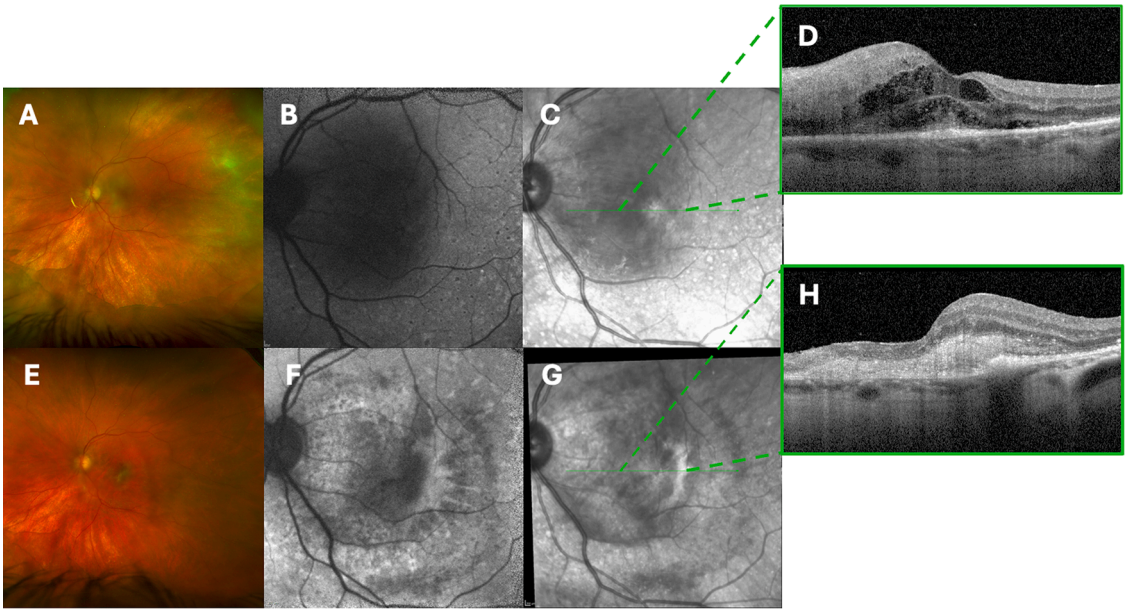

Fig. 5. Multimodal imaging of the left eye in a patient with iCNV associated with vitreoretinal lymphoma. Initial fundus photography (A) reveals a prominent whitish lesion at the posterior pole, nasal to the fovea. Blue-light fundus autofluorescence (B) demonstrates hypoautofluorescence in the same region and multifocal spots of hyperautofluorescence. Near infrared reflectance (C) also shows hyporeflectance in the posterior pole nasally to the fovea, along with spots of hyporeflectance. OCT (D) at baseline captures hyperreflective subretinal material, subretinal and intraretinal fluid. Follow-up imaging across all modalities (E, F, G, H) illustrates the development of subretinal fibrosis and resolution of intra- and subretinal fluid.

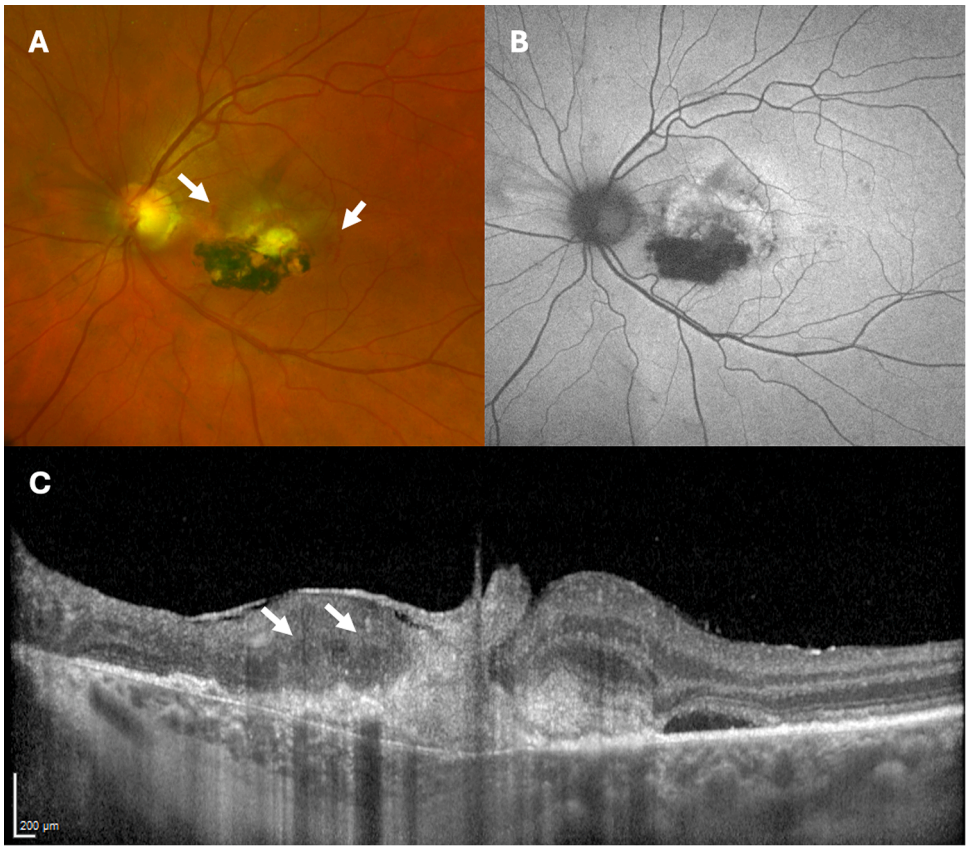

Fig. 6. Multimodal imaging of iCNV in a patient with toxoplasmic chorioretinitis. The pseudocolor fundus photograph (A) displays a pigmented atrophic lesion alongside a whitish lesion encircled by hemorrhages. Fundus autofluorescence reveals hypoautofluorescence (B) at the pigmented lesion and hyperautofluorescence at the whitish lesion. OCT (C) captures subretinal hyperreflective material indicative of iCNV, as well as outer retinal atrophy, subretinal fluid, and a thick epiretinal membrane with disorganization of the inner retinal layers.

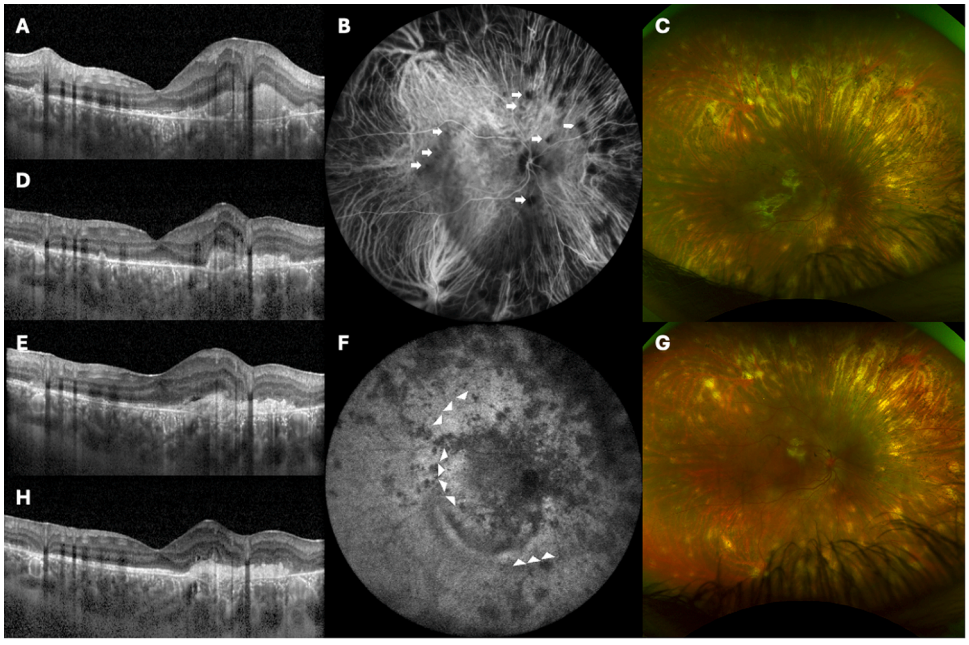

Fig. 7. Multimodal imaging of iCNV caused by syphilitic retino-choroiditis. OCT images (left column; A, D, E, H) reveal subretinal hyperreflective material indicative of iCNV, accompanied by retinal thickening and small intraretinal cysts. Indocyanine green angiography images (central column; B, F) display multiple early (B) hypofluorescent areas (arrowheads) and a prominent hyperfluorescent area in the late-phase (F) corresponding to widespread RPE and photoreceptors damage (arrows). The fundus photograph (right column; C, G) illustrates multiple yellowish lesions distributed across the posterior pole, suggestive of multifocal syphilitic retino-choroiditis.

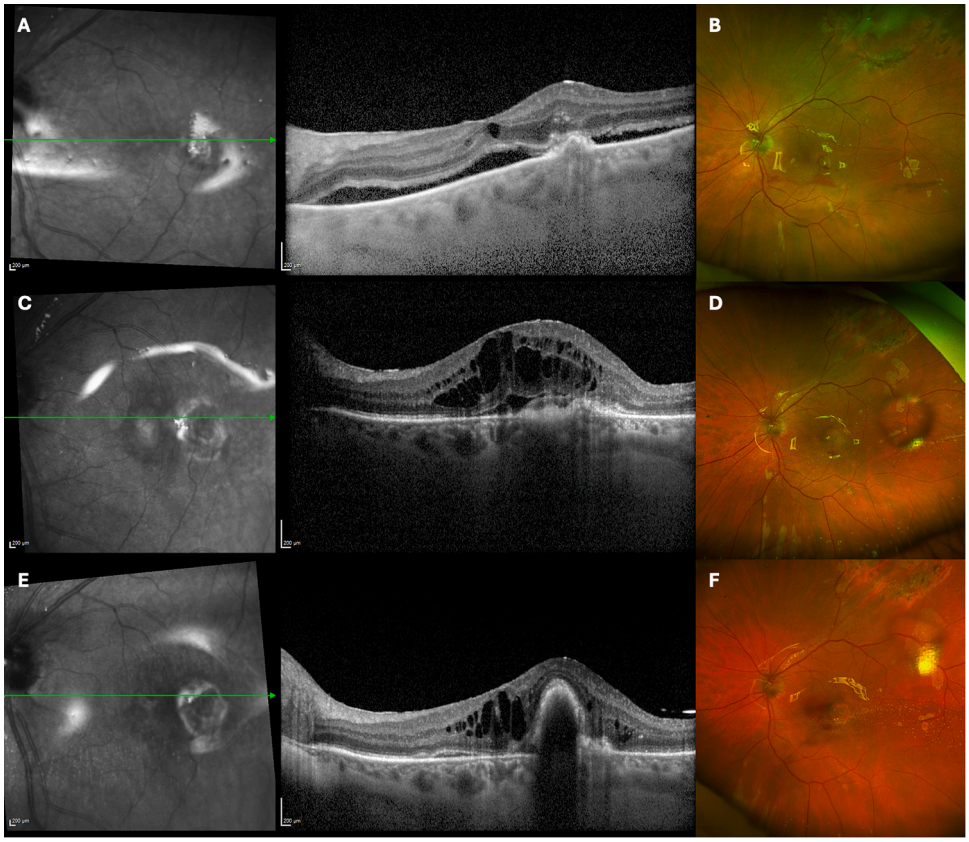

Fig. 8. Multimodal imaging of iCNV in a patient with candida endophthalmitis. Baseline OCT (A) reveals subretinal hyperreflective material indicative of iCNV, accompanied by intraretinal and subretinal fluid. The baseline ultra-widefield pseudocolor fundus photograph (B) displays silicone oil in the vitreous cavity, chorioretinal atrophy from prior retinopexy in the superotemporal periphery, and a whitish macular lesion with overlying hemorrhage. Follow-up images from the same modalities at 3 (C, D) and 6 (E, F) months document the progressive fibrosis and pigmentation of the iCNV lesion and reduction of the intraretinal fluid.

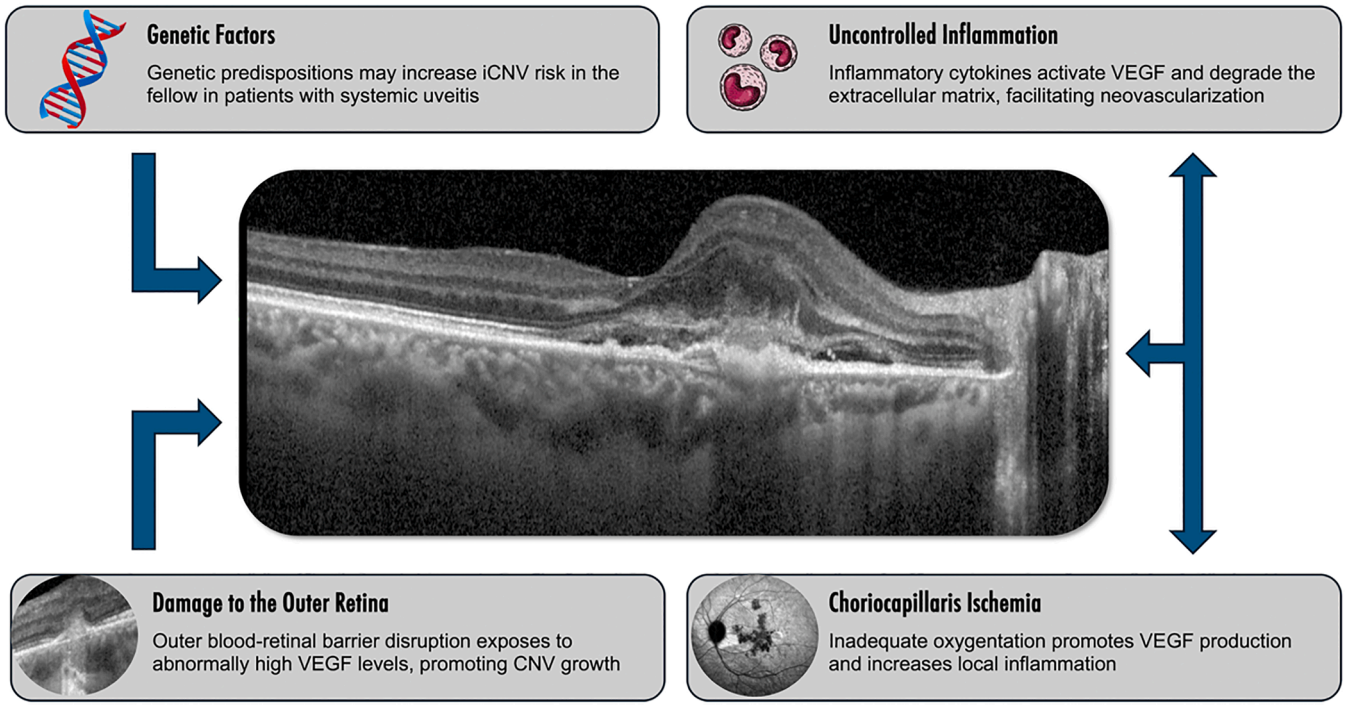

Fig. 9. Pathogenesis and risk factors of inflammatory choroidal neovascularization (iCNV).

persistent choriocapillaris ischemia, particularly in metabolically demanding areas like the fovea.[16,30,64] This mechanism aligns with placoid diseases, including APMPPE, persistent placoid maculopathy, and SC, where choriocapillaris ischemia is a primary driver of the disease.[15,19]

4.4. Damage to the outer retina

Damage to the Bruch membrane/RPE complex is another significant risk factor, particularly in conditions like PIC/iMFC, where inflammation predominantly affects these structures.[18,72,73] Damage to the Bruchmembrane/RPE complex disrupts the outer blood-retinal barrier and exposes the outer retina to abnormally high levels of VEGF, promoting neovascular tissue growth and iCNV formation. This process mirrors pathogenic mechanisms observed in other forms of CNV from mechanical stress (e.g., lacquer cracks in PM) or trauma.[4,5]

4.5. Choroidal venous insufficiency

Further contributing to the risk of iCNV, choroidal venous insufficiency observed in some eyes with posterior uveitis, such as PIC/iMFC, may promote a proinflammatory environment. Venous stasis, akin to that seen in lower extremity venous insufficiency, is characterized histologically by perivascular infiltration with monocytes, macrophages, and fibrin. Concurrently, choroidal venous insufficiency may impede the clearance of inflammatory cells and cytokines, thus enhancing localized inflammation. Although high myopes with PIC/iMFC and very thin choroids may also present with iCNV, a slightly higher prevalence has been observed in eyes with PIC/iMFC that exhibit features overlapping those of pachychoroid disease eyes.[74]

5. Multimodal imaging

Multimodal imaging is essential for the early diagnosis and management of iCNV. Clinically, iCNV may present with new-onset distortion or metamorphopsia and can lead to vision loss or scotomas that are not directly related to primary uveitis lesions. Often, iCNV lesions outside the fovea remain asymptomatic, underscoring the necessity for comprehensive imaging assessments.

5.1. Fluoresceina angiography and indocyanine green angiography

iCNV lesions, predominantly arising above the RPE, are potentially detectable on FA, appearing as focal areas of leakage and staining. FA is invaluable for detailing the extent and severity of inflammation through signs such as vascular leakage, optic nerve staining, and macular edema.[46] ICGA, on the other hand, is indispensable for diagnosing choroidal anomalies like granulomas and choriocapillaris hypoperfusion, as well as for distinguishing these findings from iCNV.[4,7] Consequently, both FA and ICGA are indispensable and should be performed at least at baseline for an accurate assessment, classification, and staging of the disease.

FA and ICGA have several limitations:

- Distinguishing iCNV from inflammatory retinochoroidal lesions using FA can be challenging due to their similar imaging characteristics.
- Extensive retinal involvement in conditions like iMFC, SC, and VKH disease can obscure hyperfluorescence, as scarring and pigmentary changes may mask underlying activity.
- Patchy chorioretinal atrophy often appears hypofluorescent on ICGA, resembling choroidal inflammatory lesions.
- Secondary photoreceptor inflammation, such as that seen in secondary MEWDS often accompanying active PIC/iMFC lesions, also appears hypofluorescent, adding another layer of complexity to image interpretation (Fig. 3).[20]

These factors underscore the necessity of integrating additional clinical data and imaging modalities to accurately identify and assess the activity of iCNV.[85]

5.2. Optical coherence tomography

iCNV typically forms between the RPE and the neurosensory retina,

displaying hyperreflective lesions above the RPE with often fuzzy margins. iCNV may also appear in a mixed form, with part of the lesion developing beneath the RPE and presenting as RPE detachments containing fibrovascular and serous components. iCNV and inflammatory lesions can coexist in the same chorioretinal area, especially in PIC/iMFC. Additionally, fibrotic and fibrovascular changes can appear alongside inflammation and active iCNV, forming what could be referred to as a "lesional complex."

The activity of iCNV is characterized by retinal thickening, subretinal or intraretinal fluid, and subretinal hyperreflective material (SHRM), which may exhibit either well-defined or ill-defined margins.[83] These features are crucial for monitoring the response to treatment.[33]

OCT is instrumental in distinguishing iCNVs from non-neovascular lesions (inflammatory or infiltrative) at the choroidal/Bruch membrane/RPE level. Studies have shown significant differences in the characteristics of PIC/iMFC lesions with and without iCNV. iCNV-associated lesions often exhibit increased volume, height, and width, along with focal elevations of the RPE, disruptions of the photoreceptors, fuzzy infiltration of the outer retina, and associated intra- or subretinal fluid. Additionally, iCNV-positive lesions show hyporeflective back-shadowing beneath the RPE, unlike iCNV-negative lesions, which display choroidal hypertransmission.[14,52,76]

Differentiating iCNV from other diseases that cause CNV, such as AMD or PM, is complex due to variations in demographic characteristics and CNV locations. In AMD, CNV typically manifests subfoveally or juxtafoveally, whereas iCNV may occur in more variable locations, including subfoveal, parafoveal, or peripapillary areas. iCNV often presents with SHRM, indicating activity, unlike the intraretinal or sub-RPE fluid accumulations typical of AMD. The "pitchfork sign" (PFS), characterized by finger-like hyperreflective projections extending from the CNV area into the outer retinal layers, is a notable but not exclusive OCT marker for iCNV.[36] While PFS is observed in noninflammatory conditions, it is more commonly associated with younger patients, likely due to stronger cohesion between the RPE and photoreceptors (Fig.s 9, 10).[94]

Furthermore, distinguishing iCNV from myopic CNV, especially when associated with PIC/iMFC, poses challenges due to overlapping demographic features and lesion locations. A key OCT characteristic that helps differentiate myopic CNV from PIC/iMFC-related iCNV is the degree of choroidal transmission; iCNV is usually associated with hypo-transmission within the lesion area and surrounding hyper-ransmission, likely reflecting inflammation-induced changes, whereas myopic CNV typically shows choroidal hypotransmission without surrounding hyper-transmission.[76]

5.3. Optical coherence tomography angiography

OCTA proves effective in delineating iCNV, similar to its utility in AMD. This modality offers a significant advantage over traditional dye angiography by providing detailed visualizations of the morphology and precise localization of iCNV lesions. A key benefit of OCTA is its ability to visualize blood flow within the neovascular network without the interference from fluorescein leakage, common in FA. This capability facilitates an accurate assessment of the lesion's depth and the involvement of different retinal and choroidal layers.[82]

Research has indicated that OCTA may aid in detecting iCNV and differentiate it from inflammatory lesions. The presence of a flow signal in iCNV, contrasted with its absence in inflammatory lesions, significantly aids in differential diagnosis.[92] For instance, Aggarwal and co-workers highlighted OCTA's effectiveness in detecting type 1 CNV in tuberculosis-associated choroiditis, a finding that FA and ICGA had failed to conclusively demonstrate due to nonspecific late-phase hyperfluorescence.[3] OCTA is also adept at detecting choroidal granulomas, highly suggestive of uveitic conditions like sarcoidosis, tuberculosis, and VKH disease, thereby aiding in the etiological diagnosis of iCNV.[70] Finally, OCTA is considered the gold standard tool for evaluating the choriocapillaris, crucial in the context of iCNV secondary to placoid diseases.[16,30]

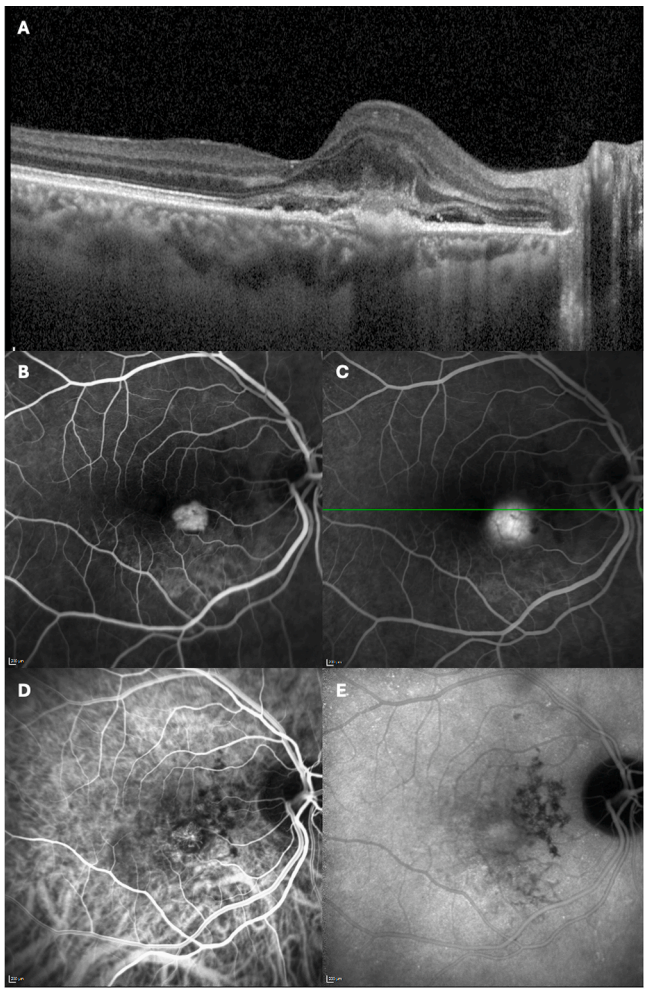

Fig. 10. Multimodal imaging of iCNV secondary to placoid disease. OCT (A) reveals subretinal hyperreflective material indicative of iCNV and the pitchfork sign, characterized by finger-like hyperreflective projections extending from the CNV area into the outer retinal layers. Fluorescein angiography highlights an area of early (B) hyperfluorescence in the macula that progresses to leakage in the late phases of the examination (C). Indocyanine green angiography displays marked hypofluorescence at the level of the choriocapillaris throughout both the early (D) and late (E) phases of the examination.

Despite its strengths, OCTA faces challenges such as motion artifacts, incorrect segmentation, and projection errors, which can complicate image interpretation. Additionally, quantitative analyses of iCNV lesions, such as area, size, vessel density, and fractal dimension, are less developed compared to those in AMD. Further studies are needed to enhance the integration of OCTA with other imaging modalities to improve overall detection and management.

6. Treatment

A variety of treatments, including focal laser photocoagulation and photodynamic therapy (PDT), have historically been employed to manage iCNV;[2] however, these therapies often come with significant side effects, and their efficacy has varied, which has limited their widespread adoption. In recent years, anti-VEGF therapies have solidified their position as the leading treatment option for iCNV due to their pronounced efficacy and favorable side effect profile.[42] Nevertheless, to effectively manage iCNV, it is imperative to address both the angiogenic and inflammatory components of the disease. While anti-VEGF therapies

are powerful, they alone are not sufficient to control the macular damage that can occur in iCNV.[87] The underlying inflammation can continue to drive neovascularization if not adequately controlled, potentially undermining the benefits of anti-VEGF treatment and leading to suboptimal outcomes.

Therefore, a comprehensive approach that includes both anti-VEGF agents and adequate immunomodulatory treatment is essential for the optimal management of iCNV. This strategy ensures that both the neovascular and inflammatory components of the disease are effectively addressed. However, the rarity of iCNV present challenges in establishing an optimal treatment regimen and in selecting the most effective therapeutic agents. The sections that follow provide detailed information for clinicians about the current drugs in use—including anti-VEGF agents, corticosteroids (CS), and immunosuppressants—highlighting their efficacy and outlining recommended treatment regimens in clinical practice.

6.1. Anti-VEGF

Anti-VEGF therapies are now considered the first-line approach in managing iCNV. Research has extensively documented the efficacy of these molecules in treating iCNV across both infectious and non-infectious uveitis.[1,2,34,37,42,47] Notably, several papers have demonstrated the efficacy of intravitreal therapy (IVT) in cases refractory to other therapies.[56,57,58] Key results from the most recent studies are summarized in Table 1.

6.1.1. Efficacy

6.1.1.1. Infectious uveitis. Significant case series involving iCNV treatments have been observed in settings such as presumed ocular histoplasmosis syndrome (POHS), toxoplasmosis, tuberculosis, and toxocariasis. Notably:

- POHS: A retrospective analysis of 28 POHS patients treated with intravitreal bevacizumab injections (including five who also received PDT) reported an improvement in visual acuity from 0.65 to 0.43 LogMar units over approximately 22.4 weeks. The addition of PDT, however, complicates the interpretation of these results.[79] In a subsequent large-scale study by Labriola and coworkers, 86 POHS patients were divided into 2 groups: 1 receiving anti-VEGF monotherapy (72 patients with aflibercept, bevacizumab, or ranibizumab) and the other receiving anti-VEGF therapy combined with either local or systemic CS (14 patients). After 1 year, both groups showed significant improvement in visual acuity (VA) and central macular thickness (CMT), with the combination therapy group demonstrating greater visual improvement. This study, however, was limited by prior treatments like PDT and the variability in CS used.[48]
- Toxoplasmosis: Korol and coworkers conducted a 12-month study involving 15 eyes from 14 patients treated with intravitreal aflibercept, noting significant improvements with VA enhancing from 0.44 to 0.19 LogMar and CMT reducing from 317 μm to 254 μm. On average, patients received 1.7 injections.[45] Smaller case series have also shown favorable outcomes with ranibizumab and bevacizumab in treating toxoplasmosis-related iCNV, also compared to other iCNVs from infectious and noninfectious uveitis.[11,80,81]
- Tuberculosis: Julian and coworkers conducted a study involving 15 patients with various forms of uveitis and iCNV, including tuberculosis-related cases, treated with intravitreal bevacizumab. Over an average of 17 months and after approximately 4.25 injections, nearly 80 % of patients noted improvements in VA and CMT.[41] Kim and coworkers reported clinical benefits in 4 patients with active iCNV due to tuberculous chorioretinitis treated with intravitreal injections of bevacizumab, ranibizumab, and aflibercept, noting that the treatments helped prevent a decline in VA.[53]
- Toxocariasis: Although cases are rarer, successful management of CNV due to toxocariasis has been achieved. Lyall and coworkers reported positive outcomes with intravitreal ranibizumab, and Yoon and coworkers described effective treatment using a combination of intravitreal ranibizumab, bevacizumab, and oral albendazole.[55,93]

6.1.1.2. Non-infectious uveitis. Anti-VEGF therapies have proven effective for managing iCNV across various non-infectious uveitis conditions, particularly PIC/iMFC, VKH disease, panuveitis, placoid diseases and intermediate uveitis.[9,22,64,86] These treatments not only improve visual outcomes but also reduce the recurrence of iCNV, especially when combined with appropriate anti-inflammatory treatments.

- PIC/iMFC: The most extensive data comes from studies on PIC/iMFC, where anti-VEGF therapies have shown significant benefits. Woronkowicz et al., in a large study involving 204 eyes, analyzed visual outcomes and found that anti-VEGF injections led to marked improvements in VA.[88] Studies by Fine and Chang and Wu evaluated the efficacy of intravitreal bevacizumab and ranibizumab, respectively, in patients with iCNV due to PIC/iMFC, showing improved VA and reduced iCNV activity.[13,29,90] Mansour and coworkers reported both short-term (30 eyes) and long-term (36 eyes) benefits of intravitreal bevacizumab in PIC/iMFC cohorts, with significant visual improvement even in cases refractory to previous treatments.[56,57]
- Stromal choroiditis: Wu and coworkers demonstrated successful outcomes using intravitreal bevacizumab for iCNV related to VKH disease in 2 patients.[89] Reports on other stromal choroiditis conditions such as BSCR and sarcoidosis are scarce, typically included in broader studies encompassing all inflammatory pathologies.
- Placoid diseases: Battaglia Parodi and coworkers evaluated the effectiveness of bevacizumab in seven eyes with iCNV related to SC, noting both functional and anatomical stabilization, with 90 % of patients preventing a decline in visual acuity and 28 % showing improvement.[68] Additionally, ranibizumab proved effective in cases of iCNV due to SC and APMPPE.[17,60]
- Intermediate uveitis: although iCNV is rare in intermediate uveitis, appearing primarily in the peripapillary area, it has responded well to bevacizumab injections in case reports by Garcia and coworkers and Mehta and coworkers showing promising functional and anatomical outcomes.[32,61]

6.1.2. Treatment regimen of anti-VEGF

6.1.2.1. Loading vs. PRN Regimens. While there is no universally accepted treatment regimen for iCNV, it is generally acknowledged that iCNV requires fewer injections than CNV secondary to other diseases, such as AMD or pathological myopia. Recent retrospective studies have provided further insights into optimal treatment strategies.

A study by Invernizzi and coworkers evaluated two distinct treatment regimens for iCNV resulting from both infectious and non-infectious causes. Patients were divided into a loading group, which received three monthly anti-VEGF injections followed by treatment as needed, and a PRN group, which received injections as needed from the start. Both groups showed significant improvements in VA, with no differences in VA gains or iCNV relapses between the groups. The loading group required a higher average number of injections (4.5) compared to the PRN group (2.5), suggesting that the PRN regimen might offer a less intensive treatment approach while still achieving similar outcomes.[40] This finding is corroborated by a study by Woronkowicz and coworkers that found no significant difference in VA improvements or iCNV relapses between patients treated with a loading dose followed by PRN versus those treated on a PRN basis from the outset.[88]

Table 1
Efficacy of Anti-Vascular Endothelial Growth Factor Therapy in Inflammatory Choroidal Neovascularization.

Study (design)	Type of uveitis (number of eyes)	Group compared / anti-VEGF agent (number of eyes injected)	Outcomes	Follow-up	Injections (range)
Infectious uveitis					
Schadlu et al. 2008[79] (retrospective)	POHS (28)	Bevacizumab (28)	VA improvement from 0.65 to 0.43 LogMar	22.4 weeks	1.8 (NA)
Korol et al. 2017[45] (prospective)	Toxoplasmosis (15)	Aflibercept (15)	VA improvement from 0.44 ± 0.46–0.19 ± 0.24 LogMar Significant CMT reduction from 317 ± 74–254 ± 43 μm	12 months	1.7 (1–2)
Labriola et al. 2023[48] (retrospective)	POHS (86)	Group 1 Anti-VEGF monotherapy (72) Group 2 Anti-VEGF + systemic/local steroids (14) *bevacizumab, ranibizumab, and aflibercept (number of eyes treated with each: NA)*	VA and CMT improvement in both groups. Significantly higher VA improvements in Group 2	12 months	Group 1: 2.9 (NA) Group 2: 3.93 (NA)
Non-infectious uveitis					
Tran et al. 2008[86] (retrospective)	PIC/iMFC (6) SC (2) SO (1) VKH (1)	Bevacizumab (10)	VA improvement from 0.62 to 0.45 LogMar Significant CMT reduction from 326 to 267 μm	7.5 months	2.5 (1–4)
Doctor et al. 2009[28] (retrospective)	BSCR (1) VKH (1) PIC/iMFC (1) SO (1) Idiopathic (1)	Bevacizumab (6)	VA improvement in 60 % of eyes	15 months	2.7 (1–5)
Fine et al. 2009[29] (retrospective)	PIC/iMFC (6)	Bevacizumab (6) Switch from bevacizumab to ranibizumab (1)	VA improvement in 5/6 eyes	41.5 weeks	2.3 (1–6)
Menezo et al. 2010[63] (retrospective)	PIC/iMFC (10)	Ranibizumab (9) Switch from ranibizumab to bevacizumab (1)	VA stabilization in 9/10 eyes	12.5 months	1.9 (1–5)
Cornish et al. 2011[22] (retrospective)	PIC/iMFC (9)	Bevacizumab (6) Ranibizumab (3)	VA gain of 0.26 LogMar	14.9 months	2.34 (1–6)
Iannetti et al. 2013[37] (retrospective)	Posterior uveitis (6) Panuveitis (2)	Bevacizumab (8)	VA improvement from 0.57 ± 0.17–0.30 ± 0.28 LogMar CMT reduction from 402.8 ± 114.1–300.5 ± 91 μm	19.2 months	3.75 (3–6)
Parodi et al. 2014[68] (prospective)	SC (7)	Bevacizumab (7)	VA improvement from 0.50 to 0.48 LogMar CMT reduction from 261 to 196 μm	12 months	1.5 (1–5)
Wu et al. 2018[90] (retrospective)	PIC/iMFC (24)	Group 1: Ranibizumab monotherapy (14) Group 2: Ranibizumab + systemic steroids (10)	VA improvement of 0.34 LogMar Fewer relapses and lower number of injections in Group 2	24 months	Group 1: 3 (1–7) Group 2: 1.9 (1–7)
Barth et al. 2018[9] (retrospective)	PIC/iMFC (16)	Bevacizumab (13) Ranibizumab (2) Switch[Ψ] (1)	VA improvement in 8/16 eyes VA stabilization in 4/16 eyes VA worsening in 4 eyes	15 months	3.5 (1–9)
Woronkowicz et al. 2022[88] (retrospective)	PIC/iMFC (174) Sarcoidosis (8) BSCR (6) SC (3) APMPPE (3) MEWDS (2) Idiopathic (2) SO (1)	Group 1 Eyes Treated with Anti-VEGF (109): • First-line (55): o Anti-VEGF monotherapy (22) o Anti-VEGF + systemic steroids/immunosuppressant (13) o Anti-VEGF + other therapies (20) *Other therapies include laser photocoagulation, PDT, and local steroids* • Non-first-line anti-VEGF therapy (54) *It is not specified which other treatment were administered or the timing of these additional treatments* Group 2 Eyes treated with other treatments (95) *Other treatments include laser photocoagulation, PDT, local and systemic steroids* *Anti-VEGF used include bevacizumab, ranibizumab, and aflibercept (number of eyes treated with each: NA)*	Outcomes Reported Exclusively for Group 1: Significantly higher VA improvement in Group 1 Fewer iCNV reactivations in eyes treated with anti-VEGF + systemic steroids/immunosuppressant	5 years	4.35 (NA)

(*continued on next page*)

Table 1 (*continued*)

Study (design)	Type of uveitis (number of eyes)	Group compared / anti-VEGF agent (number of eyes injected)	Outcomes	Follow-up	Injections (range)
Mixed causes					
Adan et al. 2007[1] (retrospective)	PIC/iMFC (5) SC (2) POHS (1) BSCR (1)	Bevacizumab (9)	VA improvement in 8/9 eyes VA stabilization in 1/9 CMT reduction in all eyes	7.1 months	1.4 (1–3)
Mansour et al. 2008[57] (retrospective)	PIC/iMFC (30) POHS (13) Idiopathic (11) VKH (5) SC (5) Vasculitis (5) Eales disease (4) Pars planitis (3) Toxoplasmosis (3) TBC (2) Sarcoidosis (2) BSCR (1)	CNV group Bevacizumab (74) NVD/NVE group Bevacizumab (11) All 84 eyes (79 patients) were refractory to the previous treatments: systemic immunosuppressant (14 patients), systemic steroids (41 patients), local steroids (19 patients), PDT (7 patients).	Outcomes Reported Exclusively for CNV group: VA improvement from 0.67 to 0.42 LogMar CMT reduction from 351 to 253 μm	3 months	1.3 (1–3)
Lott et al. 2009[54] (retrospective)	Idiopathic (5) PIC/iMFC (4) SC (2) Papillitis (2) VKH (1) Sarcoidosis (1) SO (1) Toxocariasis (1) Toxoplasmosis (1) POHS (1) CMV retinitis (1) Reactive Arthritis (1)	Bevacizumab (21 with CNV + 13 with CME) *Only information regarding CNV group is reported*	VA stabilization in CNV group	7 months	2 (1–9)
Kramer et al. 2010[47] (retrospective)	PIC/iMFC (3) POHS (2) SC (1) Panuveitis (1)	Bevacizumab (7)	VA improvement from 0.87 ± 0.74–0.38 ± 0.63 LogMar CMT reduction from 394 ± 116–254 ± 52 μm	13 months	2.7 (1–7)
Julian et al.[41] (retrospective)	PIC/iMFC (8) Placoid disease (2) SC (1) SO (1) VKH (1) TBC (1) Idiopathic (1)	Bevacizumab (15)	VA improvement from 0.53 to 0.29 LogMar CMT decrease from 239.06 to 195.20 μm	17 months	4.25 (2–8)
Rouvas et al.[77] (retrospective)	PIC/iMFC (8) VKH (4) SC (2) Scleroderma (2)	Ranibizumab (16)	VA improvement from 0.9 ± 0.4–0.6 ± 0.4 LogMar CMT reduction from 285 ± 20–233 ± 21 μm	17.6 months	2.3 (1–3)
Mansour et al. 2012[58] (retrospective)	PIC/iMFC (3) VKH (2) Toxoplasmosis (2) TBC (1)	Bevacizumab (8) All 8 eyes were refractory to the previous treatments: systemic immunosuppressant (2), systemic steroids (5), local steroids (2).	VA improvement from 0.58 to 0.20 LogMar	5 years	3 (1–15)
Mansour et al. 2012[56] (retrospective)	PIC/iMFC (36) POHS (19) SC (10) Toxoplasmosis (5) VKH (4) Vasculitis (3)	CNV group Bevacizumab (76) NVD/NVE group Bevacizumab (5) Most of the eyes were refractory to the previous treatments: systemic immunosuppressants (17), systemic steroids (31), local steroids (13).	Outcomes Reported Exclusively for CNV group: VA improvement from 0.70 to 0.25 LogMar	3 years	3 (1–31)
Roy et al. 2017[78] (retrospective)	Idiopathic (7) Toxoplasmosis (4) Panuveitis (4) VKH (4) SC (3) TBC (3) PIC/iMFC (2) Other * (3)	Bevacizumab (20) Ranibizumab (9) Switch$^{\Psi}$ (1)	VA improvement from 0.60 ± 0.49–0.40 ± 0.49 LogMar	17.9 months	2.76 (1–5)

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Table 1 (*continued*)

Study (design)	Type of uveitis (number of eyes)	Group compared / anti-VEGF agent (number of eyes injected)	Outcomes	Follow-up	Injections (range)
Sourour Zina et al.[81] (retrospective)	PIC/iMFC (12) Sarcoidosis (8) Toxoplasmosis (5) SC (5) VKH (3) POHS (2) Endophthalmitis (2) TBC (1)	Group 1: Bevacizumab monotherapy (17) Group 2: Anti-VEGF + anti-inflammatory therapy (26) (bevacizumab [n = 19], ranibizumab [n = 6], aflibercept [n = 1])	VA improvement from 0.80 to 0.51 LogMar CMT reduction from 403.7 ± 121.9–293.7 ± 82.8 μm	20.3 months	2.5 (1–13)
Invernizzi et al. 2020[40] (retrospective)	PIC/iMFC (40) Idiopathic (15) VKH (9) TBC (8) Sarcoidosis (4) Intermediate uveitis (3) Bartonella (1) DUSN (1)	LOADING group: Bevacizumab monotherapy (32) Ranibizumab monotherapy (1) Aflibercept monotherapy (3) Switch$^{\Psi}$ (6) PRN group: Bevacizumab monotherapy (29) Ranibizumab monotherapy (2) Aflibercept monotherapy (2) Switch$^{\Psi}$ (7)	VA improvements in both group with fewer infections in PRN group	24 months	LOADING group: 4.5 (3–6) PRN group: 2.5 (2–3)

This table lists studies with a sample size greater than four eyes, demonstrating the efficacy of anti-VEGF therapy in treating iCNV. The studies are ordered from oldest to most recent. Outcomes are reported as per the original paper.
Abbreviations: APMPPE: acute posterior multifocal placoid pigment epitheliopathy; BSCR: birdshot chorioretinopathy; CMV: cytomegalovirus; CMT: central macular thickness; CME: cystoid macular edema; CNV: choroidal neovascularization; DUSN: diffuse unilateral subacute neuroretinitis; NVD: neovascularization of the disc; NVE: neovascularization elsewhere; PDT: photodynamic therapy; PIC/iMFC: punctate inner choroidopathy/idiopathic multifocal choroiditis; POHS: presumed ocular histoplasmosis syndrome; SC: serpiginous choroiditis; SO: sympathetic ophthalmia; TBC: tuberculosis; VA: visual acuity; VEGF: vascular endothelial growth factor; VKH: Vogt-Koyanagi-Harada disease.
* Others include anecdotal cases of iCNV (endogenous endophthalmitis; Hansen's disease). \Ψ Switch refers to any combination of the above-mentioned drugs.

These results are consistent with the findings from the MINERVA Study, which assessed the efficacy of PRN versus sham treatments in uncommon cases of CNV, further supporting the effectiveness of PRN regimens in achieving gains in VA.[49] Additional studies by Zina and Korol have also confirmed the efficacy and safety of the PRN regimen for managing iCNV related to both infectious and non-infectious causes.[45,81]

6.1.2.2. Switcht therapy and timing. The necessity for switch therapy in iCNV treatment, often considered for cases unresponsive to initial anti-VEGF drugs, is not well-established due to the typically fewer injections required for iCNV. Hernández-Martínez and coworkers investigated the efficacy of anti-VEGF switch therapy in a small series involving patients with PIC/iMFC complicated by iCNV and persistent intraretinal fluid after 3 or more injections of ranibizumab. Unfortunately, switching to aflibercept did not yield significant improvements, underscoring the challenges and limited data available on the efficacy of switch therapy in iCNV.[35]

6.2. Corticosteroids

6.2.1. Efficacy

Research has consistently shown that managing underlying inflammation with corticosteroids, alongside anti-VEGF therapies, not only improves prognosis, but also significantly reduces the recurrence rates of iCNV. It also decreases the number of required anti-VEGF injections.[48,81,87,90] Systemic CS are particularly valued for their rapid action during acute phases.

For example, Vienne-Jumeau and coworkers observed a marked reduction in both the occurrence and recurrence of iCNV in patients with PIC/iMFC treated with high-dose systemic CS (initially 20–60 mg/day). The study highlighted that patient who developed iCNV had received considerably lower doses of systemic CS in the first 6 months following diagnosis, and those with recurrent iCNV activity were significantly less likely to have had adequate prior CS therapy.[87] Similarly, Niederer and coworkers evaluated risk factors for iCNV development in a retrospective analysis of 203 patients with PIC/iMFC. They found that patients given a high initial dose of systemic CS (>40 mg) were less likely to develop CNV.[67]

6.2.1.1. Combination therapy. Numerous studies support the efficacy of combining CS with anti-VEGF treatments. For instance, Labriola and coworkers and Wu and coworkers reported better visual outcomes and fewer recurrences in patients receiving adjuvant systemic CS for iCNV associated with POHS and PIC/iMFC, respectively, with significant improvements in VA and fewer iCNV recurrences with combined therapy.[48,90]

6.2.1.2. Local vs. systemic CS. Systemic corticosteroids are generally the preferred choice; however, the trend towards local administration is increasing. This shift is driven by the advent of long-lasting, sustained-release devices that provide prolonged efficacy with reduced side effects.[2,81]

Intravitreal CS, such as fluocinolone acetonide (FAc) and dexamethasone implants (DEX), are utilized to achieve rapid remission while minimizing systemic side effects;[50,89] however, the absence of rigorous comparative studies evaluating the effectiveness of local corticosteroids combined with anti-VEGF therapies versus anti-VEGF monotherapy still leads many clinicians to prefer systemic steroids for managing inflammation associated with iCNV. Additionally, there is still no conclusive evidence to support the preference for FAc or DEX implants as stand-alone treatments in eyes with iCNV.[71,91]

6.2.2. Limitations

6.2.2.1. Chronic use and side effects. Long-term use of CS is associated with a high risk of both systemic side effects, such as cardiovascular disease, osteoporosis, and hyperglycemia, and local side effects, including cataract formation, glaucoma, and an increased risk of infections.[6] The Multicenter Uveitis Steroid Treatment (MUST) trial indicates that maintenance doses of oral CS below 7.5 mg/day are generally considered safe;[43] however, Thorne et al. reported that while higher doses (>10 mg/day) of prednisone may reduce the risk of

structural complications associated with visual loss, lower doses (<10 mg/day) proved to be ineffective, highlighting the difficulty of balancing efficacy with safety.[84]

In long-term management, particularly after the acute phase is under control, it is recommended to transition from CS to immunosuppressants. This switch is advised due to the more favorable side effect profile and sustained anti-inflammatory effectiveness of immunosuppressants.[6,66]

6.3. Immunosuppressant

Immunosuppressants have significantly influenced the management of uveitis and were extensively utilized in treating iCNV before the introduction of anti-VEGF therapies.[26,31,65] Their role has evolved; they are now primarily used alongside anti-VEGF agents to manage underlying inflammation and prevent the recurrence of iCNV.[66]

6.3.1. Efficacy

6.3.1.1. Comparative studies on treatment approaches. Neri and coworkers explored different treatment strategies in a cohort of 39 eyes affected by iCNV due to various types of uveitis. Group A initially received high-dose systemic CS (1 mg/kg) and intravitreal anti-VEGF injections, with immunosuppressants added later as needed. Group B started treatment with high-dose systemic CS, baseline immunosuppressants agents (mycophenolate mofetil 81.3 % or cyclosporine A 18.7 %), and intravitreal anti-VEGF injections. The study revealed that Group B experienced fewer reactivations of iCNV and achieved better final VA compared to Group A, highlighting the benefits of early immunosuppressants initiation to complement their delayed effect while CS provide immediate control.[66]

A recent study by Invernizzi's group assessed the efficacy of immunosuppressants in managing iCNV. The authors compared two cohorts of patients with PIC/iMFC complicated by iCNV over a two-year period: one treated with immunosuppressants and the other with systemic CS as needed, both in conjunction with intravitreal anti-VEGF agents. The immunosuppressants cohort had a significantly lower risk of iCNV reactivation, required fewer anti-VEGF injections, and showed superior visual outcomes during the follow-up period, with mycophenolate mofetil being the predominant immunosuppressant used.[6]

These findings are supported by smaller retrospective case series, which also indicate that immunosuppressants are more effective than systemic CS alone in reducing the number of iCNV reactivations.[25,31]

6.3.1.2. Intravitreal immunosuppressants. The use of intravitreal immunosuppressants for iCNV is rare but has been explored. A case reported by Mateo-Montoya and coworkers involved a 25-year-old woman with PIC/iMFC and iCNV who responded well to a single intravitreal injection of methotrexate after receiving three injections of intravitreal ranibizumab. The patient experienced improved VA with no recurrence of the iCNV lesion at a 20-month follow-up; however, literature on intravitreal immunosuppressants for iCNV remains limited.[59]

6.3.2. Limitations

Despite increasing research into the use of immunosuppressants in conjunction with anti-VEGF agents for iCNV treatment, significant knowledge gaps remain. There are currently no standardized guidelines regarding the optimal immunosuppressant agent, the appropriate timing of treatment initiation, or criteria for switching from CS.[6,62] Moreover, managing iCNV in cases of infectious uveitis presents additional challenges, including the risk of reactivating latent infections, necessitating careful consideration of when and whether to initiate immunosuppressive therapy.[6,66]

7. Conclusion

We have examined the diagnostic and therapeutic challenges of iCNV, a major cause of vision loss associated with both infectious and noninfectious uveitis. The introduction of anti-VEGF therapies has significantly shifted the management landscape of iCNV, establishing these treatments as the primary choice due to their effectiveness and safety; however, it is important to underline that managing iCNV requires a combination of anti-VEGF and antiinflammatory therapies to effectively target both the neovascular and inflammatory aspects of the condition.

Corticosteroids are valuable for quickly managing active disease but have drawbacks, especially with long-term use. As a result, immunosuppressants are increasingly used to manage ongoing inflammation, balancing effectiveness with a better safety profile over time. The importance of starting immunosuppressive therapy early in the treatment process to prevent iCNV recurrences and manage the underlying uveitis is a key point of this review.

Despite progress, there are still significant research gaps, especially the lack of randomized clinical trials that could guide the optimal use of these therapies. Such research is necessary to fine-tune treatment strategies, determine the most effective combinations of therapies, and develop standardized treatment protocols for this complex condition.

8. Literature search

A comprehensive literature review was conducted using PubMed, covering articles published from 1979 to July 2024. The search was guided by a set of predetermined keywords: "inflammatory choroidal neovascularization," "intravitreal anti-VEGF," "posterior uveitis treatment," "non-infectious uveitis," and "infectious uveitis." The retrieved articles were screened, excluding duplicates and non-English publications, to ensure a uniform and accessible body of literature for analysis. Studies were selected based on their relevance to the topics of iCNV pathogenesis, risk factors, epidemiology, multimodal imaging, and treatment. Preference was given to studies with sample sizes greater than four, although smaller studies were included if they addressed rare diseases where larger studies were unavailable.

9. Key references

6. Airaldi M, Monteduro D, Tondini G, et al. Immunomodulatory Treatment Versus Systemic Steroids in Inflammatory Choroidal Neovascularization Secondary to Idiopathic Multifocal Choroiditis. American Journal of Ophthalmology. 2024;262:62–72.

The optimal drug to combine with anti-VEGF therapy for treating underlying inflammation and reducing iCNV recurrence is debated, with systemic steroids commonly used. However, this study demonstrates that immunosuppressants may offer comparable efficacy with a more favorable side effect profile.

10. Baxter SL, Pistilli M, Pujari SS, et al. Risk of Choroidal Neovascularization among the Uveitides. American Journal of Ophthalmology. 2013;156(3):468–77.e2.

This paper is particularly noteworthy for its reliability in reporting the prevalence and incidence of iCNV, attributed to its large sample size compared to other studies on the topic. Moreover, it provides critical information on the risk factors associated with iCNV, making it an essential reference for understanding the epidemiology of this condition.

21. Cicinelli MV, Ramtohul P, Marchese A, et al. Latest advances in white spot syndromes: New findings and interpretations. Progress in Retinal and Eye Research. 2023;97:101207.

This paper provides critical insights into the findings of white spot syndromes, including PIC/iMFC, the most frequent cause of iCNV. Understanding these findings is crucial for differentiating between inflammatory lesions and iCNV, as well as for making an etiological diagnosis of iCNV.

41. Invernizzi A, Pichi F, Symes R, et al. Twenty-four-month outcomes of inflammatory choroidal neovascularisation treated with intravitreal anti-vascular endothelial growth factors: a comparison between two treatment regimens. British Journal of Ophthalmology. 2020;104(8):1052–6.

The optimal anti-VEGF treatment regimen for patients with iCNV has been a subject of ongoing debate. This paper, despite its retrospective design, provides the first comparative analysis of two anti-VEGF treatment regimens for iCNV, offering valuable insights that could guide clinical practice.

90. Woronkowicz M, Niederer R, Lightman S, et al. Intravitreal Antivascular Endothelial Growth Factor Treatment for Inflammatory Choroidal Neovascularization in Noninfectious Uveitis. American Journal of Ophthalmology. 2022;236:281–7.

While several retrospective studies on the use of anti-VEGF for iCNV exist, this study is distinguished by its significantly larger sample size, making it valuable not only from a clinical perspective but also from an epidemiological standpoint.

Financial support

none.

Funding statement

This paper was not funded

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Maria Vittoria Cicinelli: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Elisabetta Miserocchi:** Writing – review & editing, Supervision. **Francesco Bandello:** Writing – review & editing, Supervision. **Pinar Guran Begar:** Writing – original draft. **Gloria Oldoni:** Writing – original draft. **Pierluigi Scandale:** Writing – original draft, Investigation, Data curation. **Andrea Servillo:** Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Disclosures

Francesco Bandello declares support from Alcon, Alimera Sciences, Allergan Inc, Farmila-Thea, Bayer Shering-Pharma, Bausch and Lomb, Genentech, Hoffmann-La-Roche, Novagali Pharma, Novartis, Sanofi-Aventis, Thrombogenics, Zeiss.

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