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Clinical trials and quasi-experimental studies in the treatment of noninfectious retinal vasculitis

Published in:
Survey of Ophthalmology

Publication status and date:
Accepted/In press: 01/03/2025

DOI (link to publisher):
10.1016/j.survophthal.2025.09.013

Document Version
Publisher's PDF, also known as Version of record

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Citation for the published version (APA):
Saboya-Galindo, P., Cifuentes-González, C., on behalf of ReViSe–IUSG Study Group, Rojas-Carabali, W., Mejía-Salgado, G., Le Tong, Y., Putera, I., Song, X. Y. R., Walter, C. F. Y., Shengjuan, Z., Chan, R., La Distia Nora, R., Biswas, J., Gangaputra, S., Pulido, J. S., Kempen, J. H., Nguyen, Q. D., de-la-Torre, A., Gupta, V., ... Agrawal, R. (in press). Clinical trials and quasi-experimental studies in the treatment of noninfectious retinal vasculitis: A systematic review from the International Uveitis Study Group (IUSG) Retinal Vasculitis Study (ReViSe) – Report 4. *Survey of Ophthalmology*. https://doi.org/10.1016/j.survophthal.2025.09.013

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Survey of Ophthalmology 71 (2026) 545–559

Contents lists available at ScienceDirect

Survey of Ophthalmology

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

Review article

Clinical trials and quasi-experimental studies in the treatment of noninfectious retinal vasculitis: A systematic review from the International Uveitis Study Group (IUSG) Retinal Vasculitis Study (ReViSe) – Report 4

Paola Saboya-Galindo [a,b,at], Carlos Cifuentes-González [b,c,d,at], William Rojas-Carabali [a,c,e], Germán Mejía-Salgado [b,f], Yong Le Tong [g], Ikhwanuliman Putera [h,i], Xin Ying Rachel Song [c], Cheong Fu Yuan Walter [g], Zhang Shengjuan [j], Reo Chan [g], Rina La Distia Nora [h], Jyotirmay Biswas [k], Sapna Gangaputra [l], Jose S Pulido [m,n], John H Kempen [o,p,q,r], Quan Dong Nguyen [s], Alejandra de-la-Torre [b], Vishali Gupta [t], James T. Rosenbaum [u,*], Rupesh Agrawal [a,c,e,g,v,w,**], on behalf of REVISE-IUSG study group

[a] Programme for Ocular Inflammation & Infection Translational Research, Department of Ophthalmology, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
[b] Neuroscience (NEUROS) Research Group, Neurovitae Research Center, Institute of Translational Medicine (IMT). Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia
[c] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 308433, Singapore
[d] Ocular Immunology Department, Ophthalmology Research Center, SIGMA Clinic, Cali, Singapore
[e] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[f] Colombian Visual Science and Translational Eye Research Institute (CERI), Centre of Excellence in Ocular Inflammation, Bogotá, Colombia
[g] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[h] Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Kirana Eye Hospital, Jakarta, Indonesia
[i] Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, the Netherlands
[j] Hebei Provincial Eye Hospital, Hebei Provincial Key Laboratory of Ophthalmology, Hebei Provincial Eye Institute, Xingtai, Hebei, China
[k] Department of Uvea and Ocular Pathology, Sankara Nethralaya, Chennai, Tamil Nadu, India
[l] Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, TN, USA
[m] Ocular Oncology Service, Wills Eye Hospital, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA
[n] Bower Laboratory for Translational Medicine, Vickie and Jack Farber Vision Research Center at Wills Eye Hospital, Wills Eye Hospital, Philadelphia, PA, USA
[o] Department of Ophthalmology and Schepens Eye Research Institute, Massachusetts Eye and Ear Infirmary, and Department of Ophthalmology, Harvard Medical School, Boston, MA, USA
[p] Sight for Souls, Bellevue, WA, USA
[q] MCM Eye Unit; MyungSung Christian Medical Center (MCM) Comprehensive Specialized Hospital and MyungSung Medical College, Addis Ababa, Ethiopia
[r] Department of Ophthalmology, Addis Ababa University School of Medicine, Addis Ababa, Addis Ababa, Ethiopia
[s] Spencer Center for Vision Research, Byers Eye Institute, Stanford University, Palo Alto, CA, USA
[t] Advanced Eye Centre, Post, graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[u] Legacy Devers Eye Institute, Portland, OR 97210, USA
[v] Singapore Eye Research Institute, Singapore
[w] Duke NUS Medical School, Singapore

ARTICLE INFO

Keywords:
Retinal Vasculitis
Uveitis
Behçet's Disease
Eale's Disease

ABSTRACT

This systematic review evaluates clinical trials and quasi-experimental studies reporting diagnostic criteria, disease activity scoring systems (including Disease Activity Index (DAI), Total Inflammatory Activity Index (TIAI), and Total Adjusted Disease Activity Index (TADAI), and others), and therapeutic strategies used in noninfectious retinal vasculitis (RV), aiming to consolidate current evidence on treatment response and effectiveness measures. Of 5533 articles screened (PROSPERO: CRD42023489232), 15 studies met the inclusion

* Corresponding author.
** Corresponding author at: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
E-mail addresses: Rosenbaumjames04@gmail.com (J.T. Rosenbaum), Rupesh_agrawal@ttsh.com.sg (R. Agrawal).
[as] Co-first author.

https://doi.org/10.1016/j.survophthal.2025.09.013
Received 11 April 2025; Received in revised form 13 September 2025; Accepted 15 September 2025
Available online 20 September 2025
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Disease Activity Index
Immunosuppressive Therapy

criteria. Most were conducted in Asia (73.3 %) and focused on Behçet disease (60 %) or Eales disease (27 %). RV was diagnosed clinically in all studies, while half incorporated fluorescein angiography to confirm vascular inflammation through leakage, staining, or occlusion; however, definitions of RV were highly variable, often inferred rather than explicitly stated, and lacked standardization. This diagnostic inconsistency, combined with limited imaging data, undermines comparability across studies. Disease activity was assessed using outdated composite indices such as the DAI, TIAI, and TADAI, which lack external validation and fail to capture key clinical features such as macular ischemia or capillary non-perfusion. Best corrected visual acuity, although frequently reported, was confounded by unrelated factors such as cataracts or macular scarring. Therapeutic strategies included systemic corticosteroids, immunosuppressants (e.g., methotrexate, azathioprine), and biologics (e.g., infliximab, interferon-alpha). Treatment selection was heterogeneous, and several regimens—such as cyclophosphamide-azathioprine combinations—do not align with current standards of care. Due to variability in study design and outcome reporting, no pooled effect estimates, or statistical comparisons were conducted. Treatment outcomes were synthesized descriptively based on individual study findings. Current evidence in RV clinical trials is outdated and lacks diagnostic and therapeutic standardization. There is a particular need for RV-specific definitions, validated disease activity and response indices, and contemporary therapeutic trials to guide clinical management and improve outcome comparability.

1. Introduction

Noninfectious retinal vasculitis (RV) is a sight-threatening ophthalmic condition, characterized by inflammation of the retinal vessel and/or secondary ischemia of retinal tissue that can occur as an isolated condition or in association with systemic diseases[1,37] It belongs to the category of small vessel vascular disease, and sometimes is part of systemic syndromes, but in the majority of cases, it does not meet the criteria for systemic disease.[42] RV remains a poorly understood entity owing to the lack of histopathologic evidence to establish the diagnosis.[13] Additionally, the absence of a universally accepted definition leads to different interpretations of the term "vasculitis" among ophthalmologists, rheumatologists, and other practitioners.[6,23,38]

The most widely used definition of RV is the one proposed in 2005 by the Standardization of Uveitis Nomenclature (SUN) Working Group, which states that "retinal vasculitis is considered any vascular change associated with ocular inflammation".[45] This broad definition encompasses a wide spectrum of presentations, ranging from perivascular sheathing to vascular leakage to vascular occlusions. RV has an estimated frequency of 1–2 cases per 100,000 people per year.[21] Males are affected more frequently than females.[9] RV prevalence varies significantly depending on the underlying geographical region, because RV can be associated with infectious or non-infectious diseases that exhibit ethnic and geographic predispositions.[21]

The most common presentations of (presumed) noninfectious RV include idiopathic RV, Behçet disease, sarcoidosis, Eales disease, and multiple sclerosis.[11,37] While the term “idiopathic RV” appears frequently in the literature, it remains controversial due to the lack of a universally accepted definition.[9,45] In many cases, it serves as a diagnosis of exclusion, and its use varies significantly across studies and clinical settings.[9] An additional interesting observation from one of our previous reports is that, similar to uveitis, the prevalence of RV varies by geographic region.[9] Despite this variability, a consistent finding across RV studies is that idiopathic RV (also identified by other terms such as primary RV or undifferentiated RV) accounts for approximately 38 % of reported cases (95 % CI: 26–51 %). Among secondary forms of RV due to noninfectious etiologies, RV is observed in up to 56 % of patients within Behçet disease cohorts. The geographic distribution of Behçet disease is also relevant, as it is more commonly reported in populations from Africa and Asia compared to other regions.[9]

In noninfectious forms of RV, including idiopathic, Behçet-associated, and sarcoidosis-related cases, therapeutic strategies and clinical objectives are largely similar. The primary goals of treatment are the rapid control of intraocular inflammation, prevention of recurrences, and long-term preservation of visual function.[37] Standard treatment typically involves corticosteroids (CS), either systemic or local, often in combination with immunosuppressive agents such as disease-modifying antirheumatic drugs (DMARDs). For long-term immunomodulation, biologic agents are increasingly being incorporated into management algorithms.[2,12]

There is growing interest in the early use of biologics beyond CS, particularly in light of evidence supporting the effectiveness of agents such as infliximab (IFX) or adalimumab (ADA) in ocular Behçet disease;[4,30] however, the efficacy of these therapies appears to vary by underlying etiology.[17] Similarly, anti-vascular endothelial growth factor (anti-VEGF) therapy has shown benefit in selected cases, but its role is typically limited to the management of specific complications such as macular edema or neovascularization, rather than as a primary anti-inflammatory treatment.[3] Therefore, while treatment strategies for noninfectious RV may follow a broadly similar framework, certain therapeutic choices must still be tailored based on clinical context and underlying disease characteristics.

While clinical trials and clinical studies have explored various treatment strategies and outcome measures, there is a lack of consensus on standardized frameworks for evaluating effectiveness. Recognizing these challenges, the International Uveitis Study Group (IUSG) has launched the Retinal Vasculitis Study (ReViSe). This initiative aims to consolidate and synthesize current evidence from clinical trials and quasi-experimental studies on diagnostic approaches, treatment strategies, and disease activity indices—including the Disease Activity Index (DAI), Total Inflammatory Activity Index (TIAI), Total Adjusted Disease Activity Index (TADAI), RV Severity Score, and other author-defined outcomes—to evaluate treatment response and effectiveness in noninfectious retinal vasculitis.

2. Methods

This systematic review and meta-analysis adhered to PRISMA guidelines (see Supplementary Material 1A) and was registered in PROSPERO (CRD42023489232).[34] Additional detail on methodology for this study has been reported previously.[9,10]

2.1. Search strategy

A systematic literature search was conducted on June 14, 2023, across PubMed, Embase, Cochrane (Ovid), VHL, and ProQuest. The detail search strategy was described in our previous report (see Supplementary Material 1B).[9]

2.2. Definitions

Retinal Vasculitis (RV): The SUN Working Group defines RV as “evidence of ocular inflammation and retinal vascular changes”;[45] however, given that one of the objectives of this study is to compare how RV is defined and interpreted across clinical trials, the definitions provided by the original authors of the included studies were also

considered.

Efficacy and effectiveness outcomes: Efficacy trials evaluate whether an intervention produces beneficial results under ideal and controlled conditions, while effectiveness trials measure the intervention's beneficial effects in real-world clinical settings (for different definitions of RV scoring systems see Table 1).[19,20]

2.3. Eligibility criteria

Inclusion criteria for this systematic review included scientific articles reporting randomized or, non-randomized clinical trials, and quasi-experimental study of eyes diagnosed with RV of noninfectious etiology, reporting at least one therapeutic intervention with RV definition, diagnosis, time of follow up, measurement of effectiveness or efficacy outcomes and complications. Accepted study designs only included clinical trials and quasi-experimental studies with no restrictions on language or publication date.

2.4. Selection process and data extraction

The study selection and data extraction process for this analysis have been described previously.[9] Search results were managed using Zotero® 6.0.37 (Corporation for Digital Scholarship, Vienna, Virginia, USA), with duplicate entries removed and verification performed in Microsoft Excel® 16.93 (Microsoft Corporation, Redmond, Washington, USA). Two independent reviewers screened titles and abstracts, followed by a full-text review of studies that met the predefined eligibility criteria (see above) Any disagreements were resolved through discussion or consultation with co-Principal Investigator having expertise in uveitis and/or rheumatology (RA, JTR).

Key data from the eligible studies were extracted by 2 reviewers and systematically organized in Excel (Microsoft Corporation, Redmond, Washington, USA) The extracted information included article details (author names, publication year, trial start and end dates, location, DOI, and study design), demographic characteristics (mean age ± standard deviation, and distributions of sex, diagnosis, and RV category), and intervention details (type, timing, dosage, and distributions of follow-up duration, efficacy or effectiveness outcomes, and complications).

2.5. Quality assessment

Each study was classified and appraised based on its methodological design using tools from the Joanna Briggs Institute (JBI): the Critical Appraisal Checklist for Randomized Controlled Trials (RCT) and also the same was applied to Quasi-Experimental Studies. In alignment with guidelines for assessing internal validity, we evaluated domains related to temporal precedence, selection and allocation, intervention fidelity, outcome assessment, detection and measurement bias, participant retention, and statistical conclusion validity.[36] To account for the inclusion of quasi-experimental and single-arm designs, specific items from the RCT checklist—namely, "use of true randomization" and "allocation concealment"—were deemed not applicable in studies lacking a comparator group or random sequence generation. These criteria were therefore excluded from the overall risk of bias synthesis, and the proportions reported reflect only those studies for which each criterion was applicable.

To provide a quantitative summary of methodological quality, we implemented a weighted scoring system. Each domain was scored as follows: 'Yes' = 1, 'Uncertain' = 0.5, and 'No' = 0. Domains marked 'Not applicable' were excluded from the denominator. For each study, a weighted risk of bias score was calculated by summing the assigned values for applicable domains and dividing by the number of domains

Table 1
Definitions of Retinal Vasculitis Scoring Systems.

Scores	Definition
Disease activity index(DAI)[13–15,26,31]	Dividing the fundus into four pre-equatorial and four post-equatorials segments. Only signs of active retinal vasculitis are scored. Indications of activity include the following: venous engorgement with caliber changes due to perivascular cuffing with lymphoid infiltrates; hemorrhages accompanying phlebitis; and progressive vascular occlusion, venous or arterial, following sheathing of the vessels with or without cotton-wool spots.
Total Inflammatory Activity Index (TIAI) [13–15,31]	Calculates the total inflammatory index of both eyes of the patient showing the overall inflammation. An aggressiveness coefficient was assigned depending in the impact Anterior uveitis (AU), Posterior Uveitis (PU) and Retinal Vasculitis (RV) have in the eye as they have different prognoses. For AU the coefficient was 1, for PU it was 2, and for RV it was 3. The TIAI formula was therefore: right eye ([AU x 1] + [PU x 2] + [RV x 3]) + left eye ([AU x 1] + [PU x 2] + [RV x 3]).
Total Adjusted Disease Activity Index (TADAI) [13–15,31]	Visual Acuity (VA) is added to TIAI by taking a coefficient of aggressiveness of 2. TIAI + right eye ([VA−10] x 2) + left eye ([VA−10] x 2).
Eales' disease classification system[38]	Stage 1a. Periphlebitis of small caliber vessels with superficial Stage 1b. Periphlebitis of large caliber vessels with superficial retinal hemorrhages Stage 2a. Peripheral capillary non-perfusion Stage 2b. Neovascularization elsewhere/ Neovascularization of the disc Stage 3a. Fibrovascular proliferation Stage 3b. Vitreous hemorrhage Stage 4a. Traction/ combined rhegmatogenous detachment Stage 4b. Rubeosis iridis, neovascular glaucoma, complicated cataract, and optic nerve atrophy
Retinal vasculitis scoring [40]	Made based on the number of retinal segments affected (from 1 to 8) and the severity of inflammation (mild=1, moderate=2 or severe=3). A score of 6–3 meant that 6 segments of the retinal were affected and at least 1 of these segments had a score of 3 (severe inflammation)
Fundus inflammation score[27]	The presence of any of the following will be 1 point: retinitis, retinal vasculitis, cystoid macular oedema and papillitis, maximum score of 4
Total ocular inflammation score[27]	Based on the fundus score, plus anterior chamber cells (grading of anterior chamber cells from 0 to 4) and vitreous cells (grading of vitreous cells from 0 to 4), maximum score of 12
Fabiani Grading definition[17]	FA findings into a binary grading system: 0 = no signs of active vasculitis at FA, 1 = signs of active sight-threatening retinal vasculitis.
Vallet treatment response definition [43]	Response in RV was assessed as part of a composite outcome that included clinical and treatment-related criteria. A **complete response** was defined as the full resolution of RV (absence of active inflammatory signs in the retina), along with inactive macular edema and other inflammatory manifestations, all achieved with a prednisone dose of ≤ 10 mg/day at month six. A **partial response** was considered when there was ≥ 50 % improvement in vasculitis signs or other inflammatory parameters, or significant regression of macular edema, accompanied by a ≥ 50 % reduction in corticosteroid dose. This approach provides a structured evaluation of treatment effectiveness on retinal vasculitis in a real-world clinical setting.
Bodaghi et al. response definition[8]	Response in retinal vasculitis was evaluated based on the regression of RV, which was considered a key marker of intraocular inflammation control and a major criterion for assessing treatment efficacy. The authors also applied the criteria established by the SUN Working Group

RV retinal vasculitis, TIAI Total Inflammatory Activity Index, TADAI Total Adjusted Disease Activity Index

assessed. The resulting score, ranging from 0 to 1, was interpreted as follows: ≥ 0.80 = low risk of bias, 0.50–0.79 = moderate risk, and < 0.50 = high risk. This approach enabled comparison across heterogeneous study designs while accounting for partial reporting or inapplicability of certain criteria.

2.6. Data synthesis and statistical analysis

We conducted a narrative synthesis to examine RV's demographic distribution and treatment characteristics as reported in the studies. In particular, the lack of standardized definitions for RV itself—ranging from purely clinical to angiographic criteria—and the inconsistent application of scoring systems (see Table 1) compromise the comparability of therapeutic outcomes. Moreover, this definitional heterogeneity affected the measurement of disease activity and progression, limiting our ability to synthesize results across studies. The inconsistent unit of analysis (eye-level vs patient-level) further precluded formal meta-analysis and could introduce reporting biases. Therefore, our synthesis remained qualitative, and outcome interpretations should be contextualized within these limitations. Additionally, for VA, no pooled analysis was performed due to inconsistent reporting formats across studies (Snellen, LogMAR, or unspecified). Instead, VA outcomes were summarized narratively and reported in their original format. Based on this, we did a pooled analysis of continent, number of patients, sex, mean age, number of eyes with RV, study design, primary diagnosis, definition of RV, follow-up duration just if they match on the unit of analysis. Other variables where qualitative summarized and the range of the results were presented.

3. Results

3.1. Study selection and study characteristics

Our search identified 5533 records. After removing 1241 duplicates, 4292 titles and abstracts were screened. Of these, 229 full-text articles were selected for detailed assessment. Ultimately, 15 studies met the inclusion criteria and were included in the final review (Supplementary Material 1C).[5,8,14–16,18,26–29,31,32,35,41,44] Exclusions were due to the inability to retrieve 20 articles, 188 not meeting the eligibility criteria, and 6 lacking outcomes of interest. Additional records that were initially considered for inclusion but later excluded for specific reasons are described and detailed in Supplementary Material 1D.

The final analysis included data from 499 patients with RV, after reconciling heterogeneous reporting formats across the included studies. While some publications reported patient-level data—such as Mohammadi and coworkers,[32] Kötter and coworkers,[27] and Vallet and coworkers [44] —others, including Davatchi and coworkers[16] and Davatchi and coworkers,[14] reported exclusively eye-level data. Specifically, Davatchi and coworkers[16] reported 650 eyes, and Davatchi and coworkers[14] reported 366 eyes, without providing the number of individual patients or their sex distribution. Therefore, in this systematic review, we report a total of 1488 affected eyes with RV. The mean follow-up duration was 19.1 months. The majority of studies (11/15, 73.3 %) were conducted in Asia, followed by Europe (3/15, 20.0 %) and Africa (1/15, 6.7 %) (Table 2). The most common disease studied was Behçet in 9 studies, followed by Eales disease in 4 studies. Two additional studies included patients with diverse uveitic conditions such as Vogt–Koyanagi–Harada disease, birdshot retinochoroidopathy, serpiginous choroiditis, intermediate uveitis, and idiopathic panuveitis (Table 2). The included studies varied in methodology, comprising randomized controlled trials, non-randomized interventional studies, and quasi-experimental studies. Definitions of RV were primarily clinical, though two-thirds of the studies incorporated imaging confirmation using fundus fluorescein angiography (FFA) or optical coherence tomography (OCT) (Table 2).

The RV diagnosis was based solely on clinical ophthalmological findings in 50 % of the studies, while the remaining 50 % used a combination of clinical and imaging findings, particularly FFA. Among studies on Behçet disease, 40 % (4 studies) applied clinical diagnostic criteria based on the Classification Tree and the International Criteria for Behçet's Disease (ICBD);[22] however, these did not explicitly define the criteria used for diagnosing RV, and thus a clinical diagnosis was presumed. Two additional studies on Behçet disease also used ICBD criteria, but they incorporated FFA to confirm RV diagnosis by identifying angiographic signs such as leakage, staining, and vascular occlusion.[29] Regarding Eales disease, 75 % of the studies employed FFA to identify retinal periphlebitis as part of the RV diagnosis, whereas 1 study based the diagnosis solely on clinical fundus examination and supporting laboratory data.[31]

3.2. Quality assessment risk

Risk of bias was assessed across nine key methodological domains using the JBI. Among the 15 included studies, baseline group similarity (15/15; 100 %) and adequate statistical analysis (15/15; 100 %) were universally met. Uniform and reliable outcome measurement were also consistently fulfilled (15/15; 100 %) (Supplementary Material 1E).

Allocation concealment was applicable in 5 studies, of which all (5/5; 100 %) reported appropriate methods. Blinding of participants was evaluated in 6 studies and adequately reported in only 2 (2/6; 33.3 %), while 3 studies (50 %) did not report participant blinding and one was rated as unclear. Blinding of treatment administrators was applicable in 6 studies, of which 3 (50 %) fulfilled this domain, 1 was rated uncertain, and 2 did not report any blinding. Blinding of outcome assessors was reported in 12 studies, with 10 judged as appropriate (83.3 %) and 2 unclear (16.7 %)(Supplementary Material 1E and F).

Overall, the majority of studies (14/15; 93.3 %) were rated as having low risk of bias based on domain-level numerical scores (Supplementary Material 1E and F). One study, Shalaby and coworkers, was classified as moderate risk (score = 0.78), due to absence of participant and administrator blinding. No study met criteria for high risk of bias (score <0.50). Several studies stood out for their methodological rigor: Mohammadi and coworkers[32] and Kötter and coworkers[27] fulfilled all applicable domains with a perfect score of 1.00. Uncertain ratings (0.5) were observed mainly in the domains of blinding of outcome assessors and treatment administrators in studies by Vallet and coworkers,[44] Bodaghi and coworkers,[8] Fabiani and coworkers,[18] and Markomichelakis and coworkers.[28]

3.3. Intervention characteristics

A wide range of interventions was employed across the included studies, with distinctions observed between those targeting Eales disease and Behçet' disease. For Eales disease, treatment strategies included methotrexate (MTX) as an immunosuppressive agent,[5] intravitreal bevacizumab (IVB) combined with CS and laser photocoagulation,[31] or as monotherapy focused on surgical management through pars plana vitrectomy.[26]

In Behçet's disease, immunosuppressive combinations such as MTX and CS,[16] or azathioprine (AZA) with cyclophosphamide (CP) and prednisolone,[14,32] were frequently used even in combination and named as cytotoxic combination therapy (CCT) (CP (1000 mg/monthly)+ AZA (2–3 mg/kg per day) + prednisolone (0.5 mg/kg/ daily). Biologic agents included rituximab (RTX),[15] IFX,[28,29] and ADA.[18,44] Interferon alpha-α[8,27] and cyclosporine A (CsA) combined with diltiazem [41] were also explored. Full details of each regimen and associated outcomes are provided in Tables 2 and 3.

3.4. Measurement of outcomes

Nine out of 15 studies (60 %) explicitly identified the resolution of RV as a key outcome, often using FFA to monitor vascular leakage or

Table 2
Baseline characteristics of RV clinical trials.

Authors	Location	Publication date	Start-End date	Design	Study type	Diagnosis	RV definition	Imaging definition	Patients with RV	#eyes RV	SEX: M%	Mean age	Type of intervention	Follow up mean time (months)	Intervention	Control
Eales disease																
Bali. T, et al. 2005[5]	Asia	2005	2001–2002	Single arm	Non-randomized trial	Eales disease	Clinical and imaging	Retinal periphlebitis	21	21	100	25.1	DMRADS	3	MTX 12.5 mg weekly	NA
Mehboob MA, et al.2018. [30]	Asia	2018	2015–2016	Comparative	Randomized control trial	Eales disease	Clinical		30	60	65	28.5	Anti-VEGF	NR	Group A: 3 doses of IVB (1.25mg/ 0.05ml) through pars plana approach, 4 mm from limbus using 25-gauge needle + periocular or intravitreal triamcinolone injection with peripheral laser photocoagulation and topical pressure lowering treatment	Periocular or intravitreal triamcinolone injection with peripheral laser photocoagulation and topical pressure lowering treatment.
Khanduja S, et al. 2013[25]	Asia	2013	2009–2010	Single arm	Consecutive interventional case series	Eales disease	Clinical and imaging	Retinal periphlebitis	72	76	100	26.4	Surgical	12	23 vitrectomies	NA
Patwardhan. SD, et al. 2011[34]	Asia	2011	2008–2009	Comparative	Randomized control trial	Eales disease	Clinical and imaging	Retinal periphlebitis	10	10	100	26.7	Anti-VEGF	3	BVZ intravitreal injection (1.25 mg/0.05 mL) / 4 weeks. + prophylactic topical antibiotics for 5 days after the injection	NI
Bechet disease																
Davatchi. F, et al. 2013[15]	Asia	2013	1990–2005	Single arm	Non-randomized trial	Bechet disease	Clinical		NR	650	NR	NR	DMRADS	47.9	MTX 7.5 mg weekly+ 0.5mg/ kg prednisolone	NA
Davatchi. F, et al. 2013[13]	Asia	2013	1985–1995	Single arm	Non-randomized trial	Bechet disease	Clinical		NR	366	NR	NR	Aquilant + DMRADS	NR	CP 1 g monthly pulse/6 months, then every 2–3 months + AZA 2–3 mg/kg daily + Prednisolone 0.5 mg/kg daily.	NA
Davatchi. F, et al. 2010[14]	Asia	2010	NR	Comparative	Randomized control trial	Bechet disease	Clinical	NR	20	20	65	30.9	Biologic/ DMARDS	NR	RTX vs CCT RTX: two−1000-mg courses (15-day interval)+ MTX (15 mg/ weekly) +prednisolone (0.5 mg/kg/	NA

(*continued on next page*)

Table 2 (*continued*)

Authors	Location	Publication date	Start-End date	Design	Study type	Diagnosis	RV definition	Imaging definition	Patients with RV	#eyes RV	SEX: M%	Mean age	Type of intervention	Follow up mean time (months)	Intervention	Control
															daily). CCT: CP (1000 mg/ monthly)+ AZA (2–3 mg/kg per day) + prednisolone (0.5 mg/kg/ daily).	
Mohammadi M, et al. 2017[31]	Asia	2017	NR	Comparative	Randomized control trial	Bechet disease	Clinical	NR	17	NR	76.5	30.2	IV CS	NR	1000 mg IVMP in 150 cc + 5 % D/W 1 + IV CP (1000 mg monthly) + oral AZA (2–3 mg/kg body weight daily) + prednisolone (0.5 mg/kg body weight daily)	150 cc 5 % D/W + IV CP (1000 mg monthly) + oral AZA (2–3 mg/kg body weight daily) + prednisolone (0.5 mg/kg body weight daily)
Martín-Varillas, et al. 2021. [28]	Europe	2021	NR	Single arm	Open label multicenter study	Bechet disease	Clinical and imaging	Retinal angiographic leakage, staining, and/or occlusion on FA	103	107	53	40.4	Biologic	31.5	IFX IV 3–5 mg/kg at weeks 0,2 and 6 then maintenance dose every 4–8 weeks until remission (Remission was established if there were no signs of inflammation for at lead 3 months)	NA
Shalaby U. et al 2016. [40]	Africa	2016	2010–2013	Comparative	Randomized control trial	Bechet disease	Clinical and imaging	NR	12	21	60	33	DMRADS + CCB	NR	CsA (4mg/kg) twice daily + Diltiazem (30 mg) twice daily	CsA (4mg/kg) twice daily + placebo tablets
Markomichelakis et al.(2011)[27]	Europe	2011	NR	Comparative	Randomized trial	Behçet's disease	Clinical + Fundus score	Clinical assessment + OCT	22	35	63.6	30.5	Anti-TNF vs CS	1	Infliximab 5 mg/ kg i.v. single infusion at onset of attack	High dose i.v. methylprednisolone (1 g/day × 3 days) or intravitreal triamcinolone acetonide (4 mg)
Kötter et al. (2004)[26]	Europe	2004	1995–2000	Single arm	Open prospective trial	Behçet's Disease	Clinical: panuveitis with RV	NR	50	NR	72	32	Interferon-α2a	36.4	rhIFN-α2a (initial dose 6 MIU/day, tapering)	NA
Vallet et al. (2015)[43]	Europe	2015	2001–2013	Multicenter cohort	Retrospective	Behçet's disease	SUN criteria: regression of RV signs	NR	49	NR	52	33.5	Anti-TNFα (IFX, ADA)	21	IFX 5 mg/kg or ADA 40 mg SC biweekly	No
Bechet disease and other uveitic specific conditions																
Fabiani et al, (2018)[17]	Europe	2018	2010–2017	Comparative	Retrospective cohort	Behçet's disease (patients = 35) Spondylarthritis (patients = 4)	Clinical and angiographic	Fundus examination and FA	48	82	58.3	37.96	Anti-TNFα	12	Adalimumab (40 mg fortnightly) or Infliximab (5 mg/ kg at weeks 0, 2,	None

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Table 2 (*continued*)

Authors	Location	Publication date	Start-End date	Design	Study type	Diagnosis	RV definition	Imaging definition	Patients with RV	#eyes RV	SEX: M%	Mean age	Type of intervention	Follow up mean time (months)	Intervention	Control
						Crohn's disease (patients = 1)									6, then every 8 weeks)	
Bodaghi et al. (2007)[8]	Europe	2007	NR	Retrospective	Observational	Behçet's disease (patients =23) Another chronic uveitis (patients =22) Vogt–Koyanagi–Harada (patients =2) Birdshot retinochoroidopathy (patients =2) Intermediate uveitis (patients =3) Serpiginous choroiditis (patients =1) Idiopathic panuveitis or uveo-papillitis (patients =14)	Not explicitly defined, assessed through clinical and angiographic	FA	45	40	71.1	35.6	Interferon alpha−2a	24	IFN-alpha 3 MIU, 3 times/week (initial); tapered to 3 MIU once/ week	None

ADA: Adalimumab AZA: Azathioprine BD: Behçet Disease BVZ: Bevacizumab CCB: Calcium channel blocker CP: Cyclophosphamide CS: Corticosteroids CsA: Cyclosporine A DMARDs: Disease-Modifying Anti-Rheumatic Drugs FFA: Fundus Fluorescein Angiography IFN: Interferon IFX: Infliximab IV: Intravenous IVB: Intravitreal Bevacizumab IVMP: Intravenous methylprednisolone MIU: Million International Units MTX: Methotrexate NR: Not Reported OCT: Optical Coherence Tomography RTX: Rituximab RV: Retinal Vasculitis SC: Subcutaneous SUN: Standardization of Uveitis Nomenclature TNF: Tumor Necrosis Factor

classify disease progression. Mehboob and coworkers[31] defined improvement as regression on the Eales classification scale,[39] while others lacked precise FFA-based criteria. Clinical scoring was used in 33 % (5/15) of studies, including the DAI [14–16,27,32] which evaluates RV severity across eight retinal zones. Additional inflammation metrics included the TIAI,[14–16,32] which weighs anterior, posterior, and RV involvement, and the TADAI,[14–16,32] which integrates visual acuity. Markomichelakis and coworkers[28] also used a 12-point Total Ocular Inflammation Score encompassing fundus signs and anterior/vitreous cells. Best corrected visual acuity (BCVA) was the most consistently reported endpoint, used in 14 of 15 studies (93 %) (Table 1).

Other methods included simplified grading systems such as Fabiani and coworkers[18] binary FFA classification (active vs inactive RV),[8] while Vallet and coworkers[44] applied a composite outcome definition that integrated RV remission, resolution of macular edema, and corticosteroid tapering. Bodaghi and coworkers[8] considered RV regression in alignment with SUN Working Group standards as a primary indicator of treatment success.[45] (more details Table 1).

In Eales disease, efficacy and effectiveness had been evaluated. The effectiveness data had shown that MTX monotherapy (7.5–15 mg/week orally) achieved excellent visual outcomes in 71 % of patients and remission of periphlebitis in 85.7 % over a 6-month period.[5] Furthermore, the information related to the efficacy had evidence that using a multimodal regimen combining IVB (1.25 mg/0.05 mL), triamcinolone acetonide (4 mg/0.1 mL), and laser photocoagulation reduced disease progression (34.6 % vs 69.2 % in controls) and decreased the need for vitrectomy (23.1 % vs 61.5 %) at 12 months.[31] Pars plana vitrectomy alone improved BCVA in 77.6 % of eyes with non-resolving vitreous hemorrhage.[26] In contrast, IV monotherapy (1.25 mg monthly) demonstrated limited efficacy, with poorer visual and surgical outcomes.[35]

In Behçet disease, also information related to the efficacy and effectives had shown that, in terms of effectives of non-biologic immune modulators MTX (7.5–25 mg/week orally or subcutaneously) combined with systemic CS led to BCVA improvement in 46.5 % of patients and reduction in RV activity (DAI-RV) in 53.7 %.[14] The addition of AZA (2–2.5 mg/kg/day) and CP (monthly IV pulses of 750–1000 mg/m^2) increased inflammation control (DAI-RV response in 69.7 %).[16] Regarding the evidence related to the effectiveness of biologic immune modulators it has been seen that anti-TNF agents such as IFX (5 mg/kg at weeks 0, 2, 6, then every 8 weeks), ADA (40 mg subcutaneously every other week), and interferon-α2a (3–6 million IU/day, tapered over 3–6 months) consistently demonstrated high remission rates of RV (82.6 %–94.9 %) and significant corticosteroid-sparing effects.[8,27,29,44] See Table 3 for full treatment outcomes and regimens (Table 3).

Regarding the evidence on efficacy the evidence is mainly related to biologic immunomodulators and steroidal therapy, where RTX showed a DAI RV improvement of 70 %, but BCVA improvement in only 20 %, compared to the cytotoxic group with 60 % DAI RV response and 30 % BCVA improvement.[15] High-dose IV methylprednisolone BCVA in 67.6 % and resulted in TIAI improvement in 100 %.[32] In another study it has seen that a single infusion of IFX outperformed corticosteroids in rapidly resolving posterior inflammation based of fundus score ($P < 0.0001$ for time interaction) and RV ($P < 0.003$).[28] (Table 3).

Five studies assessed RV progression in Behçet disease using composite inflammatory indices before and after treatment. Across interventions, a reduction in DAI was consistently observed, with the most pronounced improvement following high-dose IV methylprednisolone (from 4.0 to 2.2).[14–16,27,32] TIAI decreased markedly in the same study (23.0–5.7), as well as in MTX-based regimens.[14–16,32] The TADAI, which incorporates visual acuity, improved most significantly in the Intravenous methylprednisolone (IVMP) group (24.1–10.1) and in patients treated with MTX alone (25.9–19.2).[14–16,32] Although RTX and cytotoxic therapy also reduced these indices, the degree of improvement was less pronounced, particularly in the CCT group, where TADAI decreased from 43.4 to 39.8.[15] Detailed index values pre- and post-intervention for

Table 3
Main results accomplished by intervention.

Authors	Intervention	Control	Outcomes	VA format	Main results
Eales disease					
Bali. T, et al. 2005[5]	MTX 12.5 mg weekly	NA	Improvement in BCVA (Snellen) Resolution of retinal peri phlebitis with the use of FA	Snellen	• Excellent visual outcome (<6/6) was achieved in 71 % • Poor visual acuity (6/60 or worse) was achieved in 4.76 % • Effective remission of peri phlebitis (85.7 %)
Mehboob MA, et al.2018. [30]	Group A: 3 doses of IVB (1.25mg/ 0.05ml) through pars plana approach,4 mm from limbus using 25-gauge needle + periocular or intravitreal triamcinolone injection with peripheral laser photocoagulation and topical pressure lowering treatment	Periocular or intravitreal triamcinolone injection with peripheral laser photocoagulation and topical pressure lowering treatment.	Improvement in BCVA (logMAR) Vitreoretinal complications Need of PPV	LogMAR	• Progression to III or IV stage of Eales disease classification was seen in 34.6 % eyes. • Control group showed progression of disease in 69.2 %. • PPV required was 23.1 % in treatment group. • PPV required in control group 16 (61.5 %) • Stage progression: treatment group 9 (34.6 %), control 18 (69.2 %) • Regression in NV: treatment 16 (61.5 %) control 6(23.1 %) • Regression in vasculitis: treatment 14 (53.8 %) control 12 (46.2 %)
Khanduja S, et al. 2013[25]	23-gauge vitrectomy	NA	Improvement in BCVA (Snellen) Complications	Snellen	• BCVA 6/9 was achieved in 77.6 % of the cases
Patwardhan. SD, et al. 2011[34]	BVZ intravitreal injection (1.25 mg/0.05 mL) / 4 weeks. + prophylactic topical antibiotics for 5 days after the injection	NI	Resolution of vitreous hemorrhage Need of PPV	LogMAR	• BCVA better than 1.0 in 40 % study group • BCVA better than 1.0 in 70 % in control group • TDR 30 % post intervention in study group • None TDR in control group • PPV needed in 40 % of the study group • PPV needed in 20 % of the control group • Improvement of vitreous hemorrhage in 10 % study group • Improvement of vitreous hemorrhage in 20 % control group
Bechet disease					
Davatchi. F, et al. 2013[15]	MTX 7.5 mg weekly+ 0.5mg/kg prednisolone	NA	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	Snellen	• BCVA improved in 46.5 % (95 % CI=43.5 %–49.5 %) eyes • BCVA stabilization in 16.3 % (95 % CI=14.2–18.7 %) eyes • BCVA worsened in 37.2 % (95 % CI=34.3–40.2 %) eyes • DAI RV improved in 53.7 % (95 % CI=49.8 %–57.5 %) eyes • DAI RV stabilization in 16 % (95 % CI=13.4 %–19 %) eyes • DAI RV worsened in 30.3 % (95 % CI=26.9 %–33.9 %) eyes • TIAI improved in 74 % (95 % CI=70.6 %–77.2 %) patients • TIAI remained unchanged in 8.5 % (95 % CI=6.6 %–10.9 %) patients • TIAI aggravated in 17.4 % (95 % CI=14.8 %–20.5 %) patients • TADAI improved in 69.4 % (95 % CI=65.8 %–72.7 %) patients • TADAI remained unchanged in 9.1 % (95 % CI=7.1 %–11.5 %) patients • TADAI aggravated in 21.6 % (95 % CI=18.6 %–24.8 %) patients

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Table 3 (*continued*)

Authors	Intervention	Control	Outcomes	VA format	Main results
Davatchi. F, et al. 2013[13]	CP 1 g monthly pulse/6 months, then every 2–3 months + AZA 2–3 mg/kg daily + Prednisolone 0.5 mg/kg daily.	NA	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	Snellen	• BCVA improved in 44.3 % (95 % CI=39.8–48.8 %) eyes • BCVA stabilization in 21.7 % (95 % CI=18.2–25.7 %) eyes • BCVA worsened in 34 % (95 % CI=29.8–38.4 %) eyes • DAI RV improved in 69.7 % (95 % CI=64.8–74.1 %) eyes • DAI RV stabilization in 12.8 % (95 % CI=9.8–16.7 %) eyes • DAI RV worsened in 17.5 % (95 % CI=13.9–21.7 %) eyes • TIAI improved in 81.7 % (95 % CI=76.8–85.7 %) patients • TIAI remained unchanged in 6.8 % (95 % CI=4.4–10.3 %) patients • TIAI aggravated in 11.5 % (95 % CI=8.3–15.7 %) patients • TADAI improved in 71.9 % (95 % CI=66.5–76.7 %) patients • TADAI remained unchanged in 6.8 % (95 % CI=4.4–10.3 %) patients • TADAI aggravated in 21.4 % (95 % CI=17.1–26.4 %) patients
Davatchi. F, et al. 2010[14]	RTX: two−1000-mg courses (15-day interval)+MTX (15 mg/weekly) +prednisolone (0.5 mg/kg/daily).CCTG: CP (1000 mg/monthly)+ AZA (2–3 mg/kg per day) + prednisolone (0.5 mg/kg/daily).	NA	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	Snellen	• RIX BCVA improved in 20 % patients • RIX BCVA remained unchanged in 10 % patient • RIX BCVA worsened in 70 % patients • CCTG BCVA improved in 30 % patients • CCTG BCVA remained unchanged in 10 % patients • CCTG BCVA worsened in 60 % patients • RIX DAI RV improved in 70 % patients • RIX DAI RV remained unchanged in 10 % patients • RIX DAI RV worsened in 20 % patients • CCTG DAI RV improved in 60 % patients • CCTG DAI RV remained unchanged in 20 % patients • CCTG DAI RV worsened in 20 % patients • RIX TIAI improved in 90 % patients • RIX TIAI remained unchanged in 10 % patients • CCTG TIAI improved 70 % patients • CCTG TIAI remained unchanged in 20 % patients • CCTG TIAI worsened in 10 % patients • RIX TADAI improved in 90 % patients • RIX TADAI worsened in 10 % patients • CCTG TADAI improved in 70 % patients • CCTG TADAI worsened in 30 % patients
Mohammadi M, et al. 2017[31]	1000 mg IVMP in 150 cc + 5 %D/W 1 + IV CP(1000 mg monthly) + oral AZA (2–3 mg/kgbody weight daily) + prednisolone (0.5 mg/kgbody weight daily)	150 cc 5 % D/W + IV CP(1000 mg monthly) + oral AZA (2–3 mg/kgbody weight daily) + prednisolone (0.5	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	Snellen	• BCVA improved in 67.6 % (CI=16.3) eyes • BCVA stabilization in 29.5 %, (CI = 15.9) eyes • BCVA worsened in 2.9 %, (CI = 5.9) eyes

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Table 3 (*continued*)

Authors	Intervention	Control	Outcomes	VA format	Main results
		mg/kgbody weight daily)			• Control BCVA improved in (44.1 %, CI = 17.3) eyes • Control BCVA stabilization in (32.4 %, CI = 16.3) eyes • Control BCVA worsened in (2.9 %, CI = 5.9) eyes • DAI RV improved in 64.7 %, (CI = 16) eyes • DAI RV stabilization in 29.5 %, (CI = 15.3) eyes • DAI RV worsened in 5.8 % (CI = 8) eyes • Control DAI RV improved in 64.7 %, (CI = 16) eyes • Control DAI RV stabilization in 23.5.5 %, (CI = 14.1) eyes • Control DAI RV worsened in (11.8 %, CI = 10.9) eyes • TIAI improved in 100 % of the patients • Control TIAI improved in 88.2 % (CI=16.5) patients • Control TIAI worsened in (11.8 %, CI = 16.5) patients • TADAI improved in 94.1 %, (CI = 12) patients • TADAI worsened in 5.9 %, (CI = 12) patients • Control TADAI improved in (88.2 %, CI = 16.5) patients • Control TADAI worsened in (11.8 %, CI = 16.5) patients
Martín-Varillas, et al. 2021. [28]	IFX IV 3–5 mg/kg at weeks 0,2 and 6 then maintenance dose every 4–8 weeks until remission(Remission was established if there were no signs of inflammation for at lead 3 months)	NA	Improvement in BCVA (Snellen) Intraocular inflammationMacular edemaIFX optimization after remission	Snellen	• BCVA increased from a mean value of 0.44 ± 0.28 before the onset of • biologic therapy to 0.63 ± 0.28 at second year (P < 0.0001). • Improvement in AC cell count was seen in 80.4 % at 2-year follow-up. • Vitritis was only present at 2 % and the end of treatment. • Ocular remission was achieved by 76.5 % • AC cell improvement in 100 % optimized patient's vs 96.3 % non-optimized. • Vitritis improvement in 100 % optimized patient's vs 74.1 % non-optimized. • Absence of retinal vasculitis in 100 % optimized patient's vs 100 % non-optimized
Shalaby U. et al 2016. [40]	CsA (4mg/kg) twice daily + Diltiazem (30 mg) twice daily	CsA (4mg/kg) twice daily + placebo tablets	Improvement in BCVA (logMAR) Anterior chamber cell grade Vitritis score Retinal vasculitis score Optic disc swelling CME	LogMAR	• BCVA improved in study group 68.5 % cases • BCVA improved in the control group 66.7 % cases • Control group had a mean vasculitis score of 5–2, after treatment 2.2/1.3 • Study group had a mean vasculitis score of 5–2, after treatment 2/1.2
Markomichelakis et al.(2011)[27]	Infliximab 5 mg/kg i.v. single infusion at onset of attack	High dose i.v. methylprednisolone (1 g/day × 3 days) or intravitreal triamcinolone acetonide (4 mg)	Presence and resolution of retinal vasculitis (qualitative score, 0–1); Fundus inflammation score	Snellen	• Infliximab was significantly more effective than corticosteroids in clearing retinal vasculitis (P < 0.003). • At Day 29, retinal vasculitis was present in only 1 of 19 eyes (5.3 %) in the infliximab group vs 3/16 eyes (18.8 %) in the CS group. • Faster resolution of posterior inflammation (fundus score) in

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Table 3 (*continued*)

Authors	Intervention	Control	Outcomes	VA format	Main results
					the infliximab group ($P < 0.0001$ for time interaction).
Kötter et al. (2004)[26]	Human recombinant IFN-α2a (6 MIU/day SC, adjusted based on response, then tapered to 3 MIU 3x/week)	NA	Visual acuity (Snellen), remission of ocular vasculitis, steroid-sparing effect	Snellen	• VA improved from 0.56 to 0.84 by week 24 ($P < .0001$). • Long-term remission in 40 % of patients after tapering/discontinuation. • Corticosteroids reduced from mean 97 mg/day to 2 mg/day; discontinued in 81 % of responders. • Significant improvement in posterior uveitis with retinal vasculitis was observed: mean DAI reduced from 5.4 ± 3.3–1.3 ± 1.9 ($p < 0.0001$). • BCVA improved from 0.56 to 0.84 at week 24 ($p < 0.0001$). • 92 % (46/50) achieved response in ocular manifestations (posterior uveitis with retinal vasculitis).
Vallet et al. (2015)[43]	Infliximab (IFX) 5 mg/kg (wk 0, 2, 6, then q4–6wk) or Adalimumab (ADA) 40 mg q2wk ± immunosuppressive agent (AZA, MTX)	NA	Response in retinal vasculitis (CR/PR). Association with complete response. Corticosteroid-sparing effect Safety.	Not reported	• 49 patients had RV (63.6 % of those with uveitis) • Improvement in RV: 93.9 % (CR: 36.7 %, PR: 57.1 %) • IFX: RV improvement 94.9 %, ADA: 90 % • Anti-TNF mono vs combo: RV improvement 87.5 % vs 97.0 % ($p = 0.25$) • RV was significantly associated with lower odds of complete response: OR = 0.33 [0.12–0.89], $p = 0.03$ • CS dose reduced from 40 mg to 10 mg (6 mo), and 5 mg (12 mo)
		Bechet disease and other uveitic specific conditions			
Fabiani et al., (2018)[17]	Adalimumab (40 mg SC every 2 weeks) or Infliximab (5 mg/kg IV at weeks 0, 2, 6, then every 8 weeks)	NA	RV remission based on fluorescein angiography (FA) BCVA Macular edema Corticosteroid-sparing effect	Not reported	• RV remission at 3 months: 54 % • RV remission at 12 months: 86 % • Significant RV improvement from baseline to 3 and 12 months ($p < 0.0001$) • No significant difference between ADA vs IFX ($p = 0.357$) • BCVA did not significantly improve ($p = 0.950$) • Significant corticosteroid-sparing effect ($p = 0.0002$) • Macular edema resolved in 9/19 patients at 12 months ($p = 0.042$)
Bodaghi et al. (2007)[8]	Interferon alpha−2a (IFN-a2a) 3 MIU subcutaneously, 3x/week. Initiated with IV methylprednisolone pulses + oral prednisone (1 mg/kg/day).	NA	Regression of retinal vasculitis (fundoscopy + fluorescein angiography); steroid-sparing effect; visual acuity improvement.	LogMAR	• Control of retinal vasculitis achieved in 36/38 eyes (Behçet's) and 18/22 eyes (non-Behçet's), $p < 0.001$. • IFN-a2a effective in 19/23 patients with BD (82.6 %) and 13/22 with another uveitis (59 %), $p = 0.07$. • VA improved from 0.45 to 0.3 logMar (BD) and from 0.55 to 0.4 logMar (non-BD). • Relapse after IFN discontinuation occurred in 4/10 BD patients and 1/4 non-BD.

RV: retinal vasculitis, NA: not applicable, NR: not reported, NI: not intervention, MTX: methotrexate, BVZ: anti-VEGF bevacizumab, RTX: Rituximab, CCT: cytotoxic combination therapy group, IVMP: intravenous methylprednisolone, IFX: infliximab, CsA: cyclosporine A, CCB: calcium channel blocker, BCVA: Best Corrected Visual Acuity, DAI: Disease Activity Index TIAI: Total Inflammatory Activity Index, TADAI: Total Adjusted Disease Activity Index, NV: neovascularization. VA Format: Visual acuity measurement scale as reported in each study. LogMAR and Snellen values were retained as originally presented; studies that did not specify a format are marked as "Not reported."

Table 4
Comparison of Activity Indexes used as a RV Progression Outcomes in Behçet disease.

Authors	Diagnosis	Intervention	Outcomes	RV DAI PRE	RV DAI POST	TIAI PRE	TIAI POST	TADAI PRE	TADAI POST
Davatchi. F, et al. [15] (2013).	Behçet disease	MTX 7.5 mg weekly+ 0.5mg/kg prednisolone	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	2	1.4	13.3	6.6	25.9	19.2
Davatchi. F, et al.[13] (2013).	Behçet disease	CP 1 g monthly pulse/6 months, then every 2–3 months + AZA 2–3 mg/kg daily + Prednisolone 0.5 mg/kg daily.	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	3	1.4	20	8.1	28.6	18.1
Davatchi. F, et al.[14] (2010).	Behçet disease	RTX: two−1000-mg courses (15-day interval)+MTX (15 mg/weekly) +prednisolone (0.5 mg/kg/daily).	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	2.55	1.75	20.4	12.1	41.7	34.7
Davatchi. F, et al.[14] (2010).	Behçet disease	CCTG: CP (1000 mg/monthly) + AZA (2–3 mg/kg per day) + prednisolone (0.5 mg/kg/ daily).	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	2.3	2.05	20.2	16.4	43.4	39.8
Mohammadi M, et al. [31] (2017).	Behçet disease	1000 mg IVMP in 150 cc + 5 % D/W 1 + IV CP (1000 mg monthly) + oral AZA (2–3 mg/kg body weight daily) + prednisolone (0.5 mg/kg body weight daily)	Improvement in BCVA (Snellen) DAI (AU, PU, RV), TIAI, TADAI	4	2.2	23	5.7	24.1	10.1

RV: retinal vasculitis, NA: not applicable, NR: not reported, NI: not intervention, MTX: methotrexate, BVZ: anti-VEGF bevacizumab, RTX: Rituximab, CCT: cytotoxic combination therapy, IVMP: intravenous methylprednisolone, IFX: infliximab, CsA: cyclosporine A, CCB: calcium channel blocker, VA: Visual Acuity, DAI: Disease Activity Index TIAI: Total Inflammatory Activity Index, TADAI: Total Adjusted Disease Activity Index, PRE: preintervention, POST: post-intervention.

each regimen are provided in Table 4.

3.5. Adverse effects (AEs)

MTX was associated with gastrointestinal AEs such as anorexia (28.6 %), nausea (19 %), and gastric irritation (14.2 %). RTX use was linked to conjunctivitis (20 %), pneumonia, herpes zoster, and urticaria (each 10 %). High complication rates were observed following vitrectomy, including posterior subcapsular cataract (38.1 %) and intraoperative complications. IV methylprednisolone with AZA and CP caused systemic AEs such as hypertension, hyperglycemia, and cataract (each ~5.8 %). Interferon therapies (IFN-α2a and IFN-α3) were associated with flu-like syndromes, leukopenia (up to 60 %), fatigue, and liver enzyme elevation. Anti-TNF agents, particularly IFX, reported low rates of infusion reactions, while a few cases of tuberculosis and malignancy were noted. CsA caused renal and hepatic toxicity, paresthesia, and gingivitis, with variation between study and control groups. For some studies (e.g., those using ADA and combination therapy), complications were not reported. These findings are detailed in Supplementary Material 1G.

4. Discussion

We provide an overview of information from clinical investigations for treatments for RV, as well as their outcomes and complications. Among the trials that met the eligibility criteria, 2 main diseases were reported: Behçet disease and Eales disease. The diagnostic criteria for these diseases, however, as well as for RV itself, varied across studies, emphasizing the need of establishing objective definitions for RV-associated diseases.[9]

Despite their structured format, the DAI, TIAI, and TADAI scoring systems have several limitations that constrain their interpretability across studies.[14–16,27,32] While these indices were initially developed and applied in prospective trials, particularly in Behçet disease, they were constructed using arbitrarily weighted components and have not undergone comprehensive psychometric validation outside of their original clinical contexts. Key aspects such as inter-rater reliability, sensitivity to change, and applicability to non-Behçet RV subtypes remain unassessed. Furthermore, the integration of visual acuity in the TADAI introduces confounding, as VA may be influenced by factors unrelated to vasculitis activity (e.g., cataract, macular edema, retinal detachment).[14–16,32] Given the growing role of multimodal imaging in disease monitoring, the reliance on semiquantitative, predominantly fundus-based scoring systems underscores the need for updated, RV-specific indices that integrate angiographic and functional markers. A summary of the structure and limitations of these indices is provided in Supplementary Material 1H.

One of the objectives of this review was to compare outcome measurements across clinical trials and quasi-experimental studies of RV treatment. Although these indices offer a structured approach to quantify inflammation, they are largely dated and lack validation in modern clinical trials (Table 1). Their application within a single study can yield inconsistent or even contradictory findings,[31] as illustrated in the present review. For example, while high-dose IVMP showed the highest improvement in TIAI (100 %) and a stabilization rate of 29.5 % in RV DAI, no statistically significant difference was detected in TADAI scores when comparing pre- and post-treatment values for the same intervention ($P > 0.1$). These discrepancies likely reflect the limitations of using arbitrarily weighted indices that do not consistently capture the complexity of RV manifestations. The observed variability in outcomes—such as improvement with RTX (70 % in RV DAI), worsening with MTX and prednisolone (30.3 % in RV DAI and 17.4 % in TIAI), and selective response profiles depending on the index applied—highlight the influence of the scoring method on therapeutic interpretation. While these indices offer semi-quantitative insight, they must be interpreted with caution.

Importantly, none of the currently used tools captures the full spectrum of clinically relevant parameters. Also, in the binary grading system proposed by Fabiani and coworkers,[18] which categorizes FA findings as either inactive (Grade 0) or active sight-threatening vasculitis (Grade 1), does not account for intermediate disease states such as active but non-sight-threatening RV. This may limit the granularity of response assessment in clinical trials utilizing this scale.

Moreover, important features such as macular ischemia, extent of capillary non-perfusion, choroidal involvement, and the presence of retinal neovascularization are often excluded, despite their prognostic significance. Also, this approach may have led to overestimating the intervention's effect on RV regression. One example is the multimodal

phase 3 trial VISUAL I, which investigated the efficacy of ADA in patients with uveitis. This large trial included patients with RV, but its primary outcomes were not explicitly focused on RV regression but on overall disease control. Although treatment failure was defined to include new FFA findings—such as new vascular leakage or staining—there was no standardized measurement or reporting of improvement in FFA parameters. While the study provided valuable insights into the potential benefits of ADA in managing inflammatory ocular conditions, the absence of granular, RV-specific FFA outcomes underscores the need for further research focused on angiographic regression and vasculitis activity.[25]

From a clinical perspective, drawing direct comparisons between treatment outcomes in RV is inherently problematic. These limitations underscore the need for standardized, RV-specific disease activity scores that incorporate multimodal imaging, functional data, and systemic context to enhance reliability and comparability across clinical studies.

RV is potentially a sight-threatening ophthalmic disease; therefore, VA changes can be an essential outcome measure for tracking disease progression.[1,37] Still, because RV commonly occurs along with other inflammatory signs and sequelae, it is difficult to attribute changes solely to RV progression, complicating the use of VA as an outcome for RV studies. While VA appears to be an ideal and objective outcome measure, it may not reliably reflect inflammatory control. VA can be affected by unrelated factors such as cataract development, macular scarring, ocular surface dryness, or variability in testing conditions (e.g., technician technique or patient cooperation). In some cases, inflammation may fully resolve without corresponding gains in VA.

Second, RV is not a single disease entity but a manifestation of multiple underlying conditions—such as Behçet disease, Eales disease, or idiopathic forms—each with distinct pathophysiological mechanisms and therapeutic responses. Attempting to compare treatment efficacy across such heterogeneous etiologies introduces substantial confounding and limits interpretability.

Third, the current evidence in RV studies is sometimes outdated and does not reflect current standards of care. For instance, treatment regimens combining CP and AZA would be considered highly unconventional today due to overlapping toxicities and limited efficacy, particularly in diseases like Behçet where IFN-α and anti-TNF agents have largely replaced older immunosuppressants.[7,18,27,44] Similarly, although diltiazem was co-administered in one study, its purpose was to mitigate CsA-induced hypertension rather than to treat RV itself. This co-intervention complicates the interpretation of CsA's true therapeutic effect.

Furthermore, the available data on treatments like RTX in RV remain sparse and inconclusive. Also, new molecules like those targeting the IL-1 pathway in previous trials failed to meet their primary endpoints.[43]

Ultimately, therapeutic recommendations are often biased by the disease context in which the intervention was originally tested. While IFX has demonstrated excellent outcomes in Behçet-associated RV, its role in Eales disease or idiopathic RV is far less certain, and its use is contraindicated in conditions like multiple sclerosis.[33,40] These considerations reinforce the need for caution when extrapolating results across etiologies and highlight the pressing gap in high-quality, disease-specific randomized trials in RV.

5. Limitations

Regarding limitations, we acknowledge that our findings are based on a limited number of studies; nevertheless, they represent the most comprehensive available literature to date. The absence of standardized definitions for RV—ranging from purely clinical assessments to imaging-based criteria—and the inconsistent use of disease activity scoring systems (see Table 1) undermine comparability across studies. This definitional heterogeneity also affects the measurement of disease progression, limiting the feasibility of cross-study synthesis. Furthermore, the inconsistent unit of analysis (eye-level vs patient-level) introduces additional methodological complexity and precludes formal meta-analysis, potentially leading to reporting bias. For these reasons, we opted for a qualitative synthesis, and interpretations of treatment outcomes should be considered within this context.

Additionally, the variability in outcome measures and lack of validated, uniformly applied criteria may result in either overestimation or underestimation of treatment effects. On the other hand, incorporating markers other than RV progression to determine treatment effectiveness may introduce confounding bias, making it difficult to establish the true effect of the treatment on RV. Also, the use of VA as an activity index can also be seen as a confounder bias, as it can be influenced by factors noted above. Our review highlights the difficulty of heterogeneous outcome use in this field. Furthermore, given that mainly only two diseases were analyzed in the included clinical studies, the findings cannot be extrapolated to other conditions, which restricts the generalizability of our conclusions and highlights the need for further studies especially on what is often labelled as primary or idiopathic RV. Moreover, some studies have the possibility of indication-for-treatment (selection) bias. One example is when clinicians might choose MTX only for less severe cases and alkylators for more severe cases. Also, we consider that a treatment bias could be present in the studies that selected the intervention based on the known lesser amount of AEs patients could have.[24] Finally, although we applied the JBI checklists to assess methodological quality, it is important to note that there are no standardized guidelines for selecting risk-of-bias tools in the context of systematic reviews without meta-analysis. Several domains—particularly those related to randomization and allocation—were not applicable to quasi-experimental studies, which limits cross-study comparability and may overestimate quality in non-randomized designs. Nonetheless, given that our synthesis was narrative and did not combine outcomes quantitatively, the use of a formal quality appraisal framework remains appropriate for describing methodological variation across studies.

6. Conclusion

In conclusion, there is marked heterogeneity in the diagnostic criteria and objective measures used to assess disease activity and progression in RV. This intrinsic variability, coupled with the broad spectrum of underlying etiologies, reflects the difficulty to define RV as a unified clinical entity for therapeutic trials. Consequently, the development of standardized treatment approaches remains limited, and meaningful comparisons across studies are severely constrained. Although composite indices such as DAI, TIAI, and TADAI provide structured frameworks for disease assessment, their dated construction, arbitrary weighting, and inability to capture key clinical features—such as macular ischemia, extent of capillary non-perfusion, choroidal involvement, and neovascular complications—undermine their interpretative value. Our analysis also reveals that much of the available therapeutic evidence is either outdated, inconsistent, or highly context-dependent, limiting the generalizability across RV subtypes. Ultimately, the treatment landscape for RV remains a largely underexplored and fragmented field—a therapeutic desert. This striking gap underscores not only the relevance of this review, but also the urgent need for coordinated efforts like ReViSe to establish standardized diagnostic frameworks, validate modern disease activity metrics, and drive forward the development of high-quality, etiology-specific clinical trials that can meaningfully inform management strategies for RV.

This striking gap underscores not only the relevance of this review, but also the urgent need for coordinated international efforts—such as ReViSe—to develop and validate RV-specific activity indices that

incorporate multimodal imaging modalities (e.g., OCT, fluorescein/indocyanine angiography) and functional endpoints (e.g., VA, contrast sensitivity, retinal sensitivity). Future studies should prioritize the use of standardized disease definitions and outcome measures to facilitate comparability and reproducibility. In parallel, well-designed, etiology-specific clinical trials are essential to identify optimal therapeutic strategies across distinct RV phenotypes.

7. Methodology

We conducted a systematic literature search up to June 14, 2023, using PubMed, Embase, Cochrane (Ovid), VHL, and ProQuest to identify studies reporting clinical, diagnostic, laboratory, and therapeutic characteristics of RV. The search strategy incorporated terms such as "RV," "retinal periphlebitis," "treatment," "efficacy," "outcomes," and "complications," combined with diagnosis- and therapy-related keywords. Manual searches of reference lists and citation tracking were also performed to capture additional relevant studies. We included primary studies involving at least ten patients with RV, including RCTs, non-randomized clinical trials, and quasi-experimental designs, without language or publication date restrictions. Articles were excluded if they were non-full-text, animal studies, case reports, economic evaluations, systematic reviews, or relied solely on secondary data. Title and abstract screening were followed by full-text review, and data were extracted on study reference, country, patient demographics, intervention type and details, outcomes, and complications. Methodological quality was assessed using the JBI appraisal tools appropriate to study design.

Authors contributions

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

James T. Rosenbaum: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Vishali Gupta:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Rupesh Agrawal:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Rina La Distia Nora:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Reo Chan:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Carlos Cifuentes-González:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sapna Gangaputra:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation. **Paola Saboya-Galindo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation. **Jyotirmay Biswas:** Writing – review & editing, Writing – original draft, Visualization, Validation. **John H Kempen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **William Rojas-Carabali:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation. **Jose S Pulido:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Alejandra de-la-Torre:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Quan Dong Nguyen:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Yong Le Tong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation. **Germán Mejía-Salgado:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation. **Xin Ying Rachel Song:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Ikhwanuliman Putera:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Zhang Shengjuan:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Cheong Fu Yuan Walter:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation.

Funding

This study was conducted without specific funding. JTR receives support from the Rheumatology Research Foundation of the American College of Rheumatology. RA receives support from grants awarded by the National Medical Research Council (NMRC), Ministry of Health, Republic of Singapore grant number NRMC/CSAINV22jul-0004, NMRC/CSAINV19nov-0007, and NMRC/CIRG21nov-0023. JHK receives support from Sight for Souls (Bellevue, Washington, USA) and the Massachusetts Eye and Ear Global Surgery Program (Boston, Massachusetts, USA). The funders had no role in study design, data collection and analysis, publication decisions, or manuscript preparation.

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.

Acknowledgement

We thank the International Uveitis Study Group (IUSG) for their support in conducting this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.survophthal.2025.09.013.

Data availability

This study is a secondary source analysis that relied on compiling previously published information. Results can be obtained by conducting the search strategy in Supplementary Material 1B**,** and analysis indicated in the methods section with the articles stated in Supplementary Material 1D **.**

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