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Clinical Outcomes of Therapeutic Interventions for Autoimmune Retinopathy: A Meta-analysis and Systematic Review

Ishani Kapoor, BS,[1] *Swara M. Sarvepalli, MD, MS,*[2] *Dilraj S. Grewal, MD,*[3] *Majda Hadziahmetovic, MD*[3]

Topic: Autoimmune retinopathy (AIR) is a group of rare inflammatory diseases treated with immunosuppression; however, there is no treatment consensus. This meta-analysis and review aims to investigate treatment effectiveness in slowing AIR progression.

Clinical Relevance: Autoimmune retinopathy is a group of diseases characterized by progressive vision loss that is both difficult to diagnose and treat. While there is some consensus regarding diagnostic criteria, evidence-based treatment consensus remains poorly understood. Current first-line treatment is systemic steroids and conventional steroid-sparing agents. However, patients often experience treatment failure and systemic adverse effects with these medications. Understanding the effect of medications on slowing multiple visual outcomes in AIR can help to guide future treatment protocols.

Methods: PubMed, Cochrane Library, Embase, and ClinicalTrials.gov were systematically searched from inception to November 2023. Included studies treated patients with AIR with systemic, local, and biologic therapy and reported visual acuity (VA), visual field (VF), cystoid macular edema (CME), electroretinogram, central retinal thickness (CRT), and/or ellipsoid zone (EZ) loss. Risk of bias was assessed using the Critical Appraisal Skills Programme checklist. Data for meta-analysis were pooled using a random-effects model.

Results: Analysis of 40 case reports demonstrated that treatment type significantly affects the improvement of VA in patients with nonparaneoplastic retinopathy. Meta-analysis of 12 studies demonstrated that any treatment decreases the risk of progression of all 6 outcomes. Systemic therapy slows VA loss (risk ratio [RR] = 0.04, 95% confidence interval [0.00, 0.91], $P = 0.04$), VF loss (RR = 0.01, 95% confidence interval [0.00, 0.14], $P = 0.0007$), and CME (RR = 0.02, 95% confidence interval [0.00, 0.34], $P = 0.007$). Local therapy slows VA loss (RR = 0.02, 95% confidence interval [0.00, 0.12], $P < 0.00001$), CME (RR = 0.06, 95% confidence interval [0.01, 0.43], $P = 0.005$), CRT loss (RR = 0.02, 95% confidence interval [0.00, 0.36], $P = 0.007$), and EZ loss (RR = 0.31, 95% confidence interval [0.14, 0.70], $P = 0.004$). Biologics slow VA loss (RR = 0.28, 95% confidence interval [0.12, 0.65], $P = 0.003$), VF loss (RR = 0.25, 95% confidence interval [0.15, 0.42], $P < 0.00001$), and CRT loss (RR = 0.19, 95% confidence interval [0.04, 0.79], $P = 0.02$).

Conclusion: Systemic therapy significantly reduces the risk of progressive visual loss. Local therapy significantly decreases the risk of both progressive visual loss and retinal morphology loss, and therefore may offer precise targeting of the retina. Biologics significantly reduce both functional and morphological retinal changes. Immunosuppressive therapy may slow AIR progression; however, additional research is needed to assess long-term outcomes.

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Autoimmune retinopathy (AIR) is a rare inflammatory disease causing progressive visual loss, first described in 1976.[1,2] Since then, it has been characterized by the presence of antiretinal antibodies and abnormal visual field (VF) and electroretinogram (ERG) findings.[3,4] Autoimmune retinopathy can be classified as paraneoplastic, which is further divided into cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR), or as nonparaneoplastic retinopathy (npAIR).[5]

The essential diagnostic criteria for npAIR includes 5 components: no apparent cause responsible for visual function abnormality, ERG abnormality (with or without VF abnormality), serum antiretinal antibodies, absence of fundus lesions and retinal degeneration or dystrophy, and absence of overt intraocular inflammation.[6,7] Characteristic diagnostic findings are ERG with abnormalities in scotopic/photopic responses and VFs with corresponding scotomas and peripheral constrictions.[8] Despite the establishment of diagnostic criteria and the increasing

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number of published reports about this disease, there is no published standard treatment protocol.[5,9] The rarity of these disorders and lack of clinical studies providing evidence for which treatments are efficacious have prevented treatment consensus, necessitating further study.[5,9,10]

Experts agree the first-line treatment of npAIR is systemic steroids and conventional steroid-sparing agents.[8,11] Treatment of paraneoplastic retinopathy first involves treatment of a primary tumor, but additional treatment for ocular symptoms is often required.[5] Local immunosuppression with intravitreal and sub-Tenon steroid injections may also be used.[5] Multiple recent studies and case reports utilize both systemic and local therapy in addition to biologics, monoclonal antibodies, and intravenous immunoglobulin (IVIG).[5,8,9] Amongst case reports, no medication has consistently been efficacious, and there are few prospective and randomized AIR treatment studies.

Establishing treatment protocols and identifying safe and effective medications for AIR is crucial. Patients frequently need to undergo multiple medication trials before experiencing symptom stabilization while often encountering treatment failures, deterioration of vision, or systemic adverse effects. Our study has 2 objectives. First, we analyzed case report data to evaluate the impact of different treatments on an individual basis. Second, we reviewed and analyzed the existing literature by performing a meta-analysis and systematic review to assess the efficacy of systemic and local treatments in slowing AIR disease progression. We hope to provide valuable insight into the efficacy of AIR treatment through the strengths of a meta-analysis and help clinicians make treatment decisions, while emphasizing the need for prospective studies.

Methods

Eligibility Criteria for Considering Studies for This Review

Inclusion criteria for studies was defined as follows: (1) patients were diagnosed with any AIR subtype, with a diagnosis of npAIR meeting the expert consensus on diagnostic criteria, (2) patients received ≥1 medication with a minimum 1 month follow-up, and (3) before and after results were reported for at least visual acuity (VA), VF, cystoid macular edema (CME), ERG, central retinal thickness (CRT), and/or ellipsoid zone (EZ) changes. A review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024501355). This study was evaluated by the Institutional Review Board of Duke University and deemed not to require ethics approval. The study methods followed the World Medical Association Declaration of Helsinki ethical standards for medical research. Informed consent was not required as data was obtained from previously published studies.

Search Methods for Identifying Studies

A systematic literature search of PubMed, Cochrane Library, Embase, and ClinicalTrials.gov for the keywords "autoimmune retinopathy," "cancer associated retinopathy," and "melanoma associated retinopathy" was performed from inception to November 2023. A subsequent search was performed for relevant drug names, including "Ozurdex," "Iluvien," "Yutiq," "Xipere," "intravitreal Triamcinolone," "Kenalog," and "Methotrexate" in combination with the previously mentioned 3 diseases. Bibliographies of included studies were scanned for studies that may have been initially missed. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed (Fig 1).[12]

Study Selection

The inclusion/exclusion process was completed by 2 independent researchers (I.K. and S.M.S.) and any conflicts were resolved

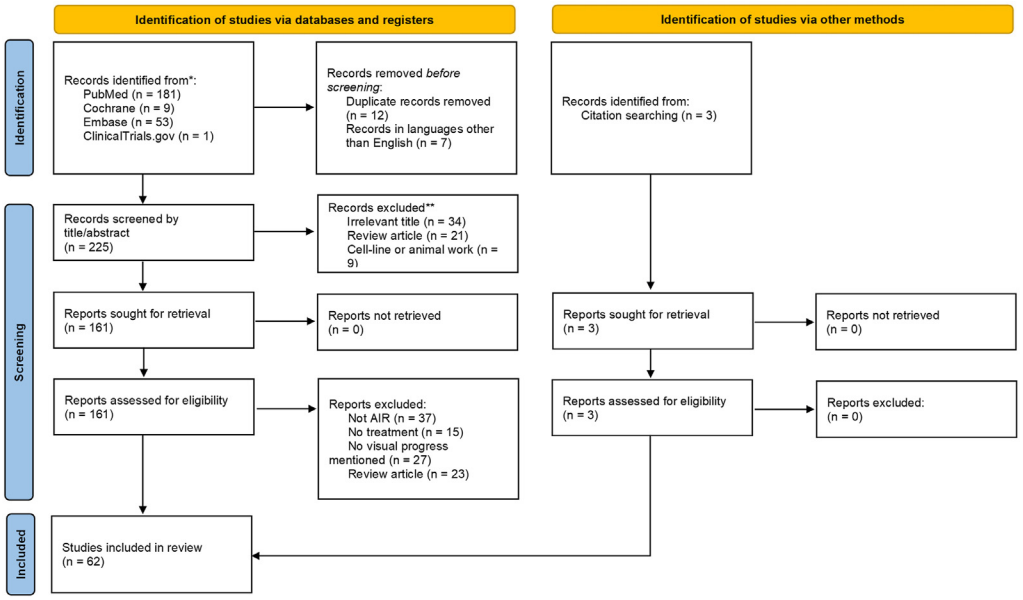

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. AIR = autoimmune retinopathy.

through discussion by a third (M.H.). Forty case reports met the inclusion criteria and were included because of the limited number of studies on this topic. This patient-level data were analyzed separately from the meta-analysis. Twelve studies, including retrospective studies and 1 clinical trial, met the inclusion criteria for meta-analysis. One of these studies included patients who also had autoimmune optic neuropathy.[13] Two case reports and 1 retrospective study were abstract only; attempts to locate a published peer-reviewed paper were unsuccessful.[14–16]

Data Collection and Risk of Bias Assessment

Data about the number of eyes in which disease improved, remained stable, or worsened with treatment were collected for 6 variables: VA, VF, CME, ERG, CRT, and EZ changes. The classification of improved, stable, or worsened was based on what was reported by the individual study. Age, sex, type of AIR diagnosis, medications used, and number of medications used were also collected. Studies were classified by treatment used. Systemic therapy included azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, prednisone, and plasmapheresis. Local therapy included intravitreal dexamethasone implant, intravitreal fluocinolone acetonide implant (Iluvien), fluocinolone acetonide implant (Retisert), sub-Tenon and intravitreal methylprednisolone acetate, and intravitreal triamcinolone acetate. Biologic agents included adalimumab, infliximab, rituximab, sarilumab, tocilizumab, and IVIG. If multiple treatments were used, the study was included in all corresponding treatment categories.

Two independent researchers (I.K. and S.M.S.) completed the search and a Risk of Bias Assessment through the Critical Appraisal Skills Programme Checklist, and then referred to a third researcher (M.H.) for review and discussion.

Data Synthesis and Analysis

Patient-level data from case reports were analyzed using Statistical Package for the Social Sciences 29.0 software. Patients were split into 3 groups by diagnosis and then classified by treatment. Chi-squared analysis determined whether improvement of visual outcomes differed based on medication class. P values <0.05 were considered statistically significant.

To determine treatment effectiveness, data for meta-analysis was categorized into progression (worsened) or no progression (stable or improved), based on the classification reported by the individual study. Studies had different definitions of improvement. Subgroup analysis was completed with the 3 treatment groups. Data for meta-analysis was pooled in Review Manager 5.4.1 using the random-effects model. Heterogeneity was evaluated by calculating the I^2 statistic and visual inspection of funnel plots for each comparison. Risk ratios (RRs) and 95% confidence intervals were calculated and P values <0.05 were considered statistically significant. The same analysis was performed to determine the RR for improvement versus stability, since these eyes were initially combined to form the category of "no progression."

Results

We screened 225 studies using our inclusion and exclusion criteria, of which 64 were obviously irrelevant. The remaining 161 studies were screened through full-text analysis. Sixty-two studies matched our inclusion criteria—40 case reports and 12 studies for meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for the selection process (Fig 1).[12]

Data from 40 case reports represents 46 patients and 86 treated eyes. Most patients experienced improvement or stability of $\geq$1 outcome (Table 1). Chi-squared analysis was used to determine if the improvement of visual outcomes varied based on the class of medication used. While the goal of AIR treatment is stabilization, using the improvement of visual parameters as the outcome ensured a sufficient number of comparisons. For patients with npAIR, medication class significantly affected the rate of improvement in VA ($P = 0.04$) (Table 2). An "n/a" indicates case reports did not report the outcome or all patients in a group improved, preventing a comparison from being run. Further logistic regression analysis was unable to be completed because of the small sample size.

The meta-analysis includes 12 studies representing 110 patients and 208 treated eyes. The average age was 54.1 $\pm$ 6.1 years, 66% were female, 75% had npAIR, 24% had CAR, and 0.9% had MAR; 39% were treated with systemic therapy, 41% with local therapy, 48% with biologic agents, and 48% were treated with >1 medication (Table 3). The mean follow-up was 26.5 $\pm$ 21.5 months. Two studies did not report age and gender demographics.[14,52] Two studies did not report the duration of follow-up.[52,61] The different definitions of improvement used by studies for the 6 outcomes of interest are shown in Table 4.

The meta-analysis was done to determine the risk of progression of visual outcomes based on medication class. All RRs are <1, indicating every medical class favors no progression (Fig 2). Systemic therapy is associated with a significantly decreased risk of progression for VA (RR = 0.04, 95% confidence interval [0.00, 0.91], $P = 0.04$), VF (RR = 0.01 [0.00, 0.14], $P = 0.0007$), and CME (RR = 0.02 [0.00, 0.34], $P = 0.007$). Treatment with local therapy is associated with a significantly decreased risk of progression for VA (RR = 0.02 [0.00, 0.12], $P < 0.00001$), CME (RR = 0.06 [0.01, 0.43], $P = 0.005$), CRT (RR = 0.02 [0.00, 0.36], $P = 0.007$), and EZ (RR = 0.31 [0.14, 0.70], $P = 0.004$). Treatment with biologic agents is associated with a significantly decreased risk of progression for VA (RR = 0.28 [0.12, 0.65], $P = 0.003$), VF (RR = 0.25 [0.15, 0.42], $P < 0.00001$), and CRT (RR = 0.19 [0.04, 0.79], $P = 0.02$).

Since "no progression" included both patients that remained stable or improved, the analysis was repeated, parsing out the difference in stability and improvement to determine if medication class influences whether visual outcomes remain stable or improve. Local therapy is associated with a significantly higher risk of improvement in CRT (RR = 43.00 [2.77, 666.52], $P = 0.007$); however, this represents 1 study (Fig 3). Other associations that favor improvement are systemic therapy on VF, local therapy on VF, and biologic agents on CME and EZ, though these failed to achieve statistical significance. Systemic therapy and biologic agents both significantly favor stability of VA (RR = 0.19 [0.07, 0.53] and RR = 0.25 [0.10, 0.67], respectively) and ERG readings (RR = 0.16 [0.04, 0.63] and RR = 0.26 [0.07, 0.89], respectively). Local therapy significantly favors stability of EZ (RR = 0.07 [0.01, 0.46], $P = 0.006$).

Table 1. Patient-Level Data from Case Reports

Study	Follow-Up (Mo.)	Age/ Sex	Diagnosis	Therapy	VA	VF	CME	ERG	CRT	EZ
Abraham, 2017[10]	18	25/F	npAIR	S	Stable OU	Improved OU				
Breunig, 2012[17]	11	19/F	npAIR	S, L	Stable OU	Improved OU		Stable OU		Stable OU
Bursztyn, 2015[18]	12	64/M	npAIR	S		Improved OU		Improved OU		
Choi, 2016[19]	4	40/M	npAIR	S	Worsened OU	Worsened OU				
DiLoreto, 2014[16]	12	87/M	npAIR	L	Stable OU					
Eton, 2020[20]	n/a	57/F	npAIR	S, B	Improved OU	Improved OU	Improved OU			
Finn, 2020[21]	48	46/F	npAIR	B	Improved OU		Improved OU			Improved OU
Fox, 2015[7]	60	53/F	npAIR	S, B	Improved OU	Stable OU		Improved OU		Stable OU
Grewal, 2021[22]	18	29/F	npAIR	B	Improved OU	Stable OD, improved OS	Improved OU	Improved OU		
Idrees, 2020[15]	24	87/M	npAIR	L	Stable OU					Stable OU
Uludag, 2016[23]	6	58/M	npAIR	B	Improved OU			Improved OU		
Zhou, 2023[24]	7	49/F	npAIR	S		Worsened OU		Stable OU		
Andrikopoulou, 2023[25]	3	67/F	CAR (ovarian)	S, B	Improved OU			Improved OU		
Bordin, 2023[26]										
Patient 1	24	58/F	CAR (lung)	L	Stable OU	Stable OU		Stable OU		
Patient 2	n/a	66/M	CAR (renal)	L	Stable OU	Stable OU		Stable OD, worsened OS		
Brossard-Barbosa, 2023[27]	4	70/M	CAR (bladder)	S	Stable OD, improved OS					
Chaves, 2023[28]	12	66/F	CAR (breast)	L	Improved OS					
DiLoreto, 2014[16]	6	64/M	CAR (lung)	L	Stable OU					
Dy, 2013[29]	18	61/F	CAR (uterine)	S, B	Improved OU	Improved OU				
Espandar, 2007[30]	96	66/F	CAR (breast)	B	Improved OU	Improved OU				
Guy, 1999[2]										
Patient 1	1	62/F	CAR (lung)	S	Improved OU					
Patient 2	1	77/F	CAR (cervical)	S	Stable OU	Improved OU				
Patient 3	1	71/M	CAR (pancreas)	S	Stable OD	Improved OD				
Huynh, 2012[31]	31	67/M	CAR (lung)	L	Improved OU		Improved OU			
Idrees, 2020[15]										Stable OD
Patient 1	6	64/M	CAR (lung)	L	Stable OD	Stable OD				Stable OU
Patient 2	13	68/F	CAR (breast)	L	Stable OU	Worsened OU				
Kim, 2019[32]	6	64/M	CAR (lung)	S, L	Improved OU	Stable OU				
Liu, 2013[33]	4	58/M	CAR (Waldenstrom macroglobulinemia)	S	Stable OU			Improved OU		
Moyer, 2014[34]	36	67/M	CAR (lung)	L	Stable OU	Stable OU	Improved OD, stable OS			
Mudri, 2021[35]	2	65/F	CAR (lung)	L	Improved OU	Improved OU		Improved OU		
Oohira, 2007[36]	180	65/M	CAR (lung)	S, L	Stable OU	Stable OU				
Or, 2013[37]	4	51/F	CAR (adrenal)	B	Improved OD, stable OS					
Roels, 2017[38]	23	45/F	CAR (ovarian)	S, B	Improved OU	Improved OU		Improved OU		
Saito, 2012[39]	3	73/F	CAR (colon)	S, L	Improved OU				Improved OU	

Table 1. (Continued.)

Study	Follow-Up (Mo.)	Age/ Sex	Diagnosis	Therapy	VA	VF	CME	ERG	CRT	EZ
Wagley, 2020[40]	n/a	84/F	CAR (renal)	S	Stable OU	Worsened OU		Improved OU		
Abou-Samra, 2021[41]	15	63/M	MAR	L	Improved OU			Improved OU	Improved OU	
Evoy, 2020[42]	24	63/M	MAR	S		Stable OU				
Hamdan, 2022[43]	36	65/M	MAR	L, B	Improved OU			Improved OU		
Hung, 2022[44]	4	83/M	MAR	S	Improved OU	Stable OU		Stable OU		
Jacobzone, 2004[45]	11	70/F	MAR	S		Improved OU		Improved OU		
Karatsai, 2019[46]	36	73/F	MAR	L	Improved OU	Improved OU		Improved OU		
Kellner, 1995[47]	48	44/M	MAR	S	Improved OU	Stable OU		Stable OU		
Lin, 2023[48]	24	47/F	MAR	L	Improved OU	Improved OU		Improved OU		
Peeters, 2023[49]	n/a	72/F	MAR	S	Improved OD	Improved OD		Improved OD		
Poujade, 2021[50]	36	68/F	MAR	L	Improved OU			Improved OU		
Subhadra, 2008[51]	19	56/M	MAR	S	Improved OU	Improved OU		Stable OU		

B = biologic agents; CAR = cancer-associated retinopathy; CME = cystoid macular edema; CRT = central retinal thickness; ERG = electroretinogram; EZ = ellipsoid zone; F = female; L = local therapy; M = male; MAR = melanoma-associated retinopathy; npAIR = nonparaneoplastic retinopathy; OD = right eye; OS = left eye; OU = both eyes; S = systemic therapy; VA = visual acuity, VF = visual field. n/a indicates follow-up time was not reported.

Discussion

Autoimmune retinopathy is a rare immune-mediated disease characterized by antiretinal antibodies driven by photoreceptor damage with variable but generally poor visual prognosis.[62] While immunosuppressive therapy is considered the basis of treatment, there is no evidence-based consensus on the efficacy and safety of these interventions.[21] A review of the current literature yields multiple studies and case reports reporting varying success in treating both npAIR and paraneoplastic AIR.

Case Reports: Individual Patient Data

Because of the large number of published case reports, we first looked at the effect of treatment on this patient group, which generally experienced stability or improvement of visual outcomes (Table 1). Chi-squared analysis revealed that in patients with npAIR, improvement of VA significantly differs by treatment class. However, this comparison includes 9 eyes, which is small to make definitive conclusions. Furthermore, change in VA is a difficult variable to follow because of variable presentations of VA in patients with npAIR. Most npAIR case reports noted improvement in ERG with systemic treatment.[17,18,24] One study reported a patient with worsening VA and VF despite systemic and local treatment, which the authors attributed to treatment initiation after significant destruction of retinal photoreceptors.[19] Two case reports used intravitreal fluocinolone acetonide implants, due to inability to tolerate systemic immunosuppression, and reported stabilization of VA.[15,16] Local therapy may be preferred for those experiencing systemic side effects. More specifically, surgical fluocinolone acetonide implants, which are used to replace the need for long-term systemic steroids, may be a good choice on their own or as an adjunct to biologic agents.

Treatment of npAIR with biologics demonstrated improvement in VA and VF.[20,23,62] Both rituximab, which targets B cells, and interleukin-6 (IL-6) inhibitors treated CME-associated npAIR.[20–22] One case report described a patient who experienced visual decline with multiple immunosuppressive therapies until starting rituximab, and within 1 month the VA and ERG improved.[7] Biologics are often used after patients have failed systemic therapy. Therefore, it is difficult to conclude if there is some synergistic effect between previously used medications. The general success of these medications indicates biologics should be considered for the treatment of refractory AIR. Researching these agents may provide insight into disease pathogenesis.

Paraneoplastic subtypes are first treated by treating the underlying malignancy, though this rarely improves visual outcomes because antibodies are already in circulation and persist after remission, requiring additional treatment.[26,34,40] Most patients with CAR were treated with systemic therapy and local treatment was used if unable to tolerate systemic therapy.[28] One patient demonstrated a strong response to intravitreal dexamethasone; the vision worsened after treatment wore off and improved shortly after another

Table 2. Effect of Treatment on Visual Outcomes from Case Report Data

	VA Improved	P Value	VF Improved	P Value	ERG Improved	P Value	EZ Improved	P Value
Treatment of npAIR		0.04		0.659		0.290		0.261
Systemic therapy	0/2		2/4		1/2		n/a	
Local therapy	0/2		n/a		n/a		0/1	
Biologic agents	3/3		1/1		2/2		1/1	
Systemic & local therapy	0/1		1/1		0/1		0/1	
Systemic therapy & biologic agents	2/2		1/2		1/1		0/1	
Treatment of CAR		0.137		0.096		0.155		
Systemic therapy	2/6		2/3		2/2		n/a	n/a
Local therapy	3/9		1/6		1/3		2/2	
Biologic agents	2/2		1/1		n/a		n/a	
Systemic & local therapy	2/3		0/2		n/a		n/a	
Systemic therapy & biologic agents	3/3		2/2		2/2		n/a	
Treatment of MAR		n/a		0.206		0.117		
Systemic therapy	4/4		3/6		2/5		n/a	
Local therapy	4/4		2/2		4/4		n/a	
Systemic therapy, biologic agents, & local therapy	1/1				1/1		n/a	

CAR = cancer-associated retinopathy; ERG = electroretinogram; EZ = ellipsoid zone; MAR = melanoma-associated retinopathy; npAIR = nonparaneoplastic retinopathy; VA = visual acuity, VF = visual field.

dose.[31] Another patient treated solely with intravitreal dexamethasone as first-line had improved VA, VF, and ERG.[35] In CAR specifically, local treatments may be preferred if patients are on multidrug regimens or immunosuppressed. Intravitreal dexamethasone is thought to be a good choice as its drug profile is similar to a pulse administration of systemic steroids.[26]

The pathophysiology of MAR is poorly understood and occurs in patients with cutaneous melanoma.[50] First-line therapy is removal of the primary tumor and reduction of metastatic disease.[6] If visual symptoms persist, then systemic steroids and plasmapheresis are added.[6] Patients in case reports were treated with systemic and local therapy, and biologics were used in 1 patient. Hamdan et al reported successful treatment with rituximab, IVIG, and intravitreal corticosteroids, resulting in a full return of VA and ERG responses.[43] Some research suggests treatment of melanoma with immune checkpoint inhibitors may contribute to MAR; further research is needed to determine if local medication can mitigate this effect.

Table 3. Demographics of Patients Included in Meta-Analysis

Demographic Characteristics	All Patients (N = 110)
Age (Yrs)	54.1 ± 6.1
Sex (%)	
Male	43
Female	66
Diagnosis (%)	
npAIR	75
CAR	24
MAR	0.9
Medicine used (%)	
Systemic therapy	39
Local therapy	41
Biologic agents	48
Number of medicines used (%)	
1	52
>1	48
Mean follow-up (mos)	26.5 ± 21.5

CAR = cancer-associated retinopathy; MAR = melanoma-associated retinopathy; npAIR = nonparaneoplastic retinopathy.

Meta-Analysis: Study Level Data

A meta-analysis of published studies was done to evaluate the efficacy of multiple classes of medications in treating AIR, which provided evidence that systemic therapy significantly reduces the risk of progression of functional outcomes like VA, VF, and CME. Local therapy additionally significantly reduces the risk of progression of retinal-specific outcomes like CRT and attenuation of the EZ, in addition to VA and CME.

Two included studies, using first-line treatments of systemic steroids and conventional steroid-sparing agents, reported stability in VA and ERG readings.[54,60] These studies also suggested ERG is a sensitive measure to reveal the underlying retinal dysfunction, track disease progression, and monitor for response to treatment.[54,60] In patients with worsening symptoms despite treatment, ERG may be a more objective method, compared with VA and VF, to track progress. Fundus autofluorescence images were commonly obtained at baseline but were not consistently tracked through the course of treatment. Hou et al reported resolution of inflammatory reaction on both OCT and fundus autofluorescence after local treatment with intravitreal dexamethasone implant, but reported constriction of the inner boundary of hyper-autofluorescent ring with disease progression, consistent with loss of EZ on OCT and ERG deterioration.[56]

Ferreyra et al used systemic and local therapies and found that immunosuppression resulted in clinical improvement and patients with CAR were most responsive to treatment, while patients with npAIR were least

Table 4. Definition of Improvement of Visual Outcomes

Outcome	Improvement Defined as:
Visual acuity	• Gain of ≥2 lines on the Snellen chart compared with baseline[13,52–55] • Gain of ≥25% of visual acuity[56] • Ratio of posttreatment to pretreatment response >1[57]
Visual field	• At least 2 dB increase in mean deviation on Humphrey visual field[56,58] • At least 3 dB increase in mean deviation on Humphrey visual field[55,59] • Expansion of the visual field by ≥25% compared with baseline[53]
CME	• Resolution of CME[53,56,57]
Electroretinogram	• At least 25% gain of amplitudes in at least half of the parameters[13,55,59,60] • At least 40% gain of amplitude in ≥1 parameter[56,58] • Ratio of posttreatment to pretreatment response >1[57]
Central retinal thickness	• At least 20% reduction in thickness in the setting of CME[52] • No change in thickness in the absence of CME[52,57] • Subjective assessment of reduction per the authors[58]
Ellipsoid zone	• Measurable recovery of ellipsoid zone loss as seen on SD-OCT[52] • Qualitative evaluation of ellipsoid zone on SD-OCT by authors[54]

CME = cystoid macular edema; dB = decibel; SD-OCT = spectral-domain OCT.

responsive.[53] Another study using intravitreal dexamethasone implants found that CME and retinal inflammation improved after 1 injection.[56] They also reported stability or improvement in VA, VF, ERG response, and the EZ.[56] The patients with disease worsening had 2 to 4 years longer disease duration, similar to other studies regardless of medication choice.[56] Local therapy may potentially improve retinal morphology, leading to better visual outcomes, and offers the advantage of minimal systemic side effects. The growing evidence of local therapy improving the markers of retinal damage highlights the necessity for rigorous evaluation to ascertain their efficacy and safety profile.

Biologic agents successfully slowed loss of VA and VF and retinal morphology, such as CRT. Damage and destruction of retinal tissue by antiretinal antibodies is thought to be the basis of the pathophysiology of AIR.[3] Therefore, monoclonal antibodies like rituximab, which

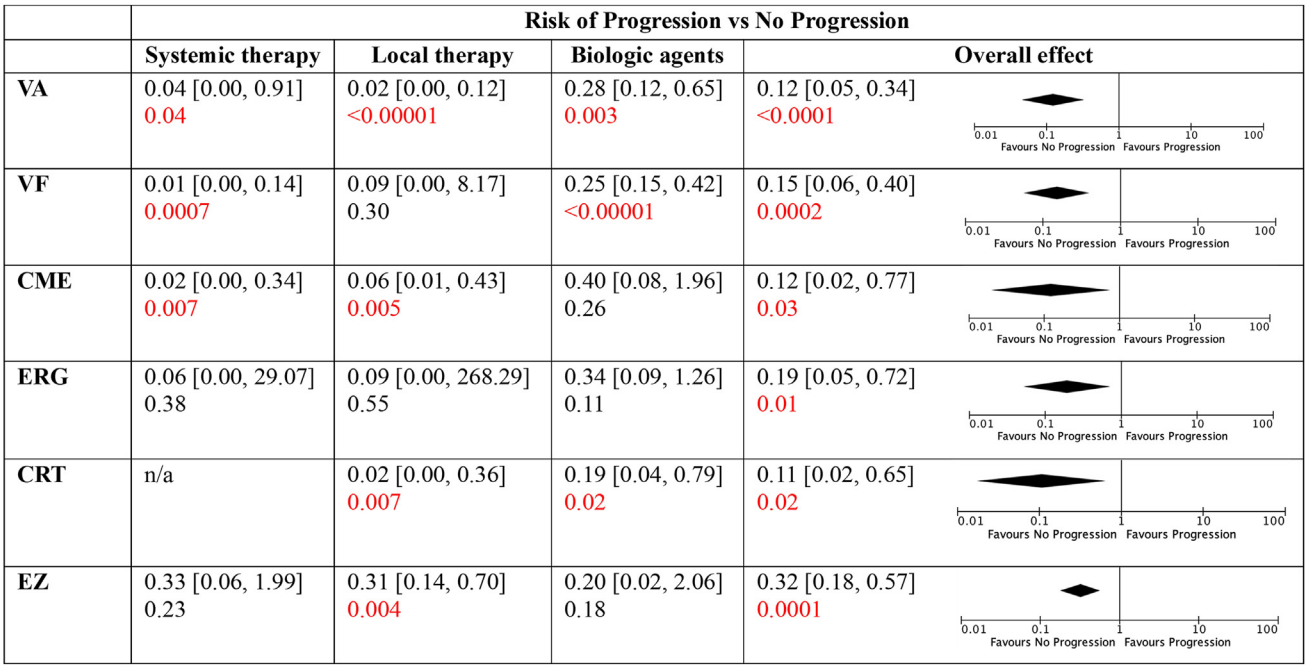

Figure 2. Progression vs. no progression of visual outcomes by treatment type.[13,14,52–61] CME = cystoid macular edema; CRT = central retinal thickness; ERG = electroretinogram; EZ = ellipsoid zone; VA = visual acuity, VF = visual field.

	Risk of Improvement vs Stabilization			
	Systemic therapy	**Local therapy**	**Biologic agents**	**Overall effect**
VA	0.19 [0.07, 0.53] 0.001	0.42 [0.08, 2.34] 0.32	0.25 [0.10, 0.67] 0.006	0.25 [0.14, 0.46] <0.00001
VF	1.02 [0.40, 2.65] 0.96	1.24 [0.17, 8.87] 0.83	0.20 [0.03, 1.18] 0.08	0.70 [0.37, 1.30] 0.25
CME	0.83 [0.46, 1.51] 0.55	0.91 [0.52, 1.60] 0.74	1.93 [0.16, 23.47] 0.61	1.03 [0.56, 1.88] 0.93
ERG	0.16 [0.04, 0.63] 0.009	0.37 [0.01, 9.89] 0.55	0.26 [0.07, 0.89] 0.03	0.23 [0.10, 0.55] 0.83
CRT	n/a	43.00 [2.77, 666.52] 0.007	0.73 [0.06, 8.57] 0.80	2.13 [0.18, 25.70] 0.55
EZ	0.50 [0.07, 3.55] 0.49	0.07 [0.01, 0.46] 0.006	2.40 [0.03, 175.59] 0.69	0.59 [0.09, 3.92] 0.58

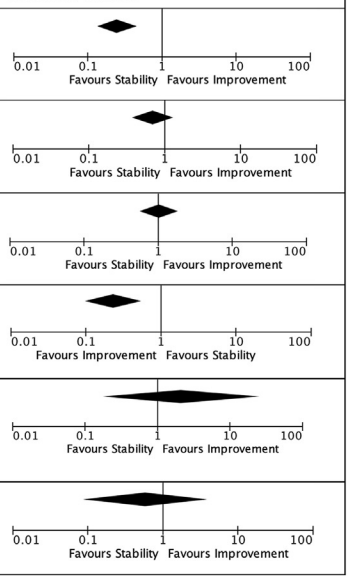

Figure 3. Improvement vs. stability of visual outcomes by treatment type.[13,14,52–61] CME = cystoid macular edema; CRT = central retinal thickness; ERG = electroretinogram; EZ = ellipsoid zone; VA = visual acuity, VF = visual field.

targets B cells, and tocilizumab and sarilumab, which target IL-6, are increasingly being studied due to their ability to reduce systemic antibody levels.[52,57,58] Eight of the 12 studies used biologic agents—5 used rituximab, 1 used IL-6 inhibitors (tocilizumab and sarilumab), 2 used bortezomib, and 2 used IVIG.[13,14,52,55,57–59,61] Two included studies found that patients with shorter disease duration and earlier initiation of the treatment with rituximab were more likely to have stabilization, and often improvement, of VA.[58,59] Several studies documented patients who previously failed to improve with first-line agents prior to initiating a biologic agent.[13,55,57–59] Boudreault et al proposed that individuals who exhibited limited response to rituximab and failed prior immunomodulatory treatment may have possessed a restricted number of functional photoreceptors.[57] Another study demonstrated that in patients with continued loss of EZ integrity while on multiple systemic and local immunomodulatory therapy, treatment with anti-IL-6 agents led to the recovery of the EZ, improvement in VA, and eventually, reduction in the burden of systemic immunomodulatory therapy.[52] While individual studies demonstrate variable responses to biologics, the meta-analysis suggests a more consistent benefit in treating AIR.

Cystoid macular edema-associated AIR was frequently studied. Data suggest AIR with CME is a more severe form of retinal disease compared with AIR without CME.[21,60] Safadi et al reported eyes with CME had extinct ERG at presentation and abnormal fundoscopic exam, OCT, and VF defects.[60] Both systemic and local therapy resulted in a significantly decreased risk of progression of CME. Ferreyra et al demonstrated that patients with npAIR experienced resolution of CME with systemic and local immunosuppression and greater visual improvement than patients without CME.[53] Furthermore, Ferreyra et al suggested that immunosuppression may be the best choice of treatment for rebound failures when treating CME since the action of the medication is directed at the cause of the condition.[53] Multiple studies reported CME resolution with biologics, both rituximab and anti-IL-6 agents.[13,52,57] The standard of CME care is steroids; thus, resolution with immunosuppression is expected. However, since patients also experience CME resolution with biologics, there may be an alternate pathophysiology for the development of CME in npAIR. These agents may offer supplementary advantages in repairing retinal damage associated with AIR pathology.

Medication adverse effects may guide treatment choice. Among studies using systemic therapy, only Ferreyra et al reported that 10 of 30 patients discontinued ≥1 medication due to adverse events.[53] Specifics were not reported and no events were attributed to local therapy.[53] Hou et al reported 4 eyes developed increased intraocular pressure and 2 eyes developed posterior subcapsular opacity, which were successfully managed and intravitreal dexamethasone was continued.[56] Common adverse events with biologics included infusion reactions, leukopenia, and infections. Davoudi et al reported that 6 of 16 patients experienced one of these events, but with treatment, rituximab was continued. Armbrust et al reported 3 of 5 patients with mild rituximab infusion reactions.[59] Boudreault et al reported 1 of 5 patients stopped rituximab due to recurrent sinusitis.[57] Maleki et al reported 1 of 6 patients stopped therapy due to dermatitis, leukopenia, and peripheral neuropathy but was on both rituximab and cyclophosphamide.[13] Maleki et al reported no significant adverse effects for all 6 patients.[55]

Limitations

Limitations can be attributed to AIR being a rare disease and the limited standardized studies with transparent discourse of diagnostic criteria. Studies often had different primary outcomes and definitions of improvement and stability, affecting the dataset's rigor. Because of the lack of consensus on treatment, patients were often treated with evolving medication regimens. Furthermore, patients often had a history of treatment failure before being included in the study. Therefore, residual effects from long-acting medications may complicate the interpretation of treatment effects. Each medication group (systemic therapy, local therapy, and biologic agents) contained different medication brands. Comparisons of efficacy within the same medication class were unable to be completed due to the small study sizes. This is an important area for future study as it is possible that medications within the same class have different effects. Follow-up times varied and some studies noted patients initially improved and then worsened. Standardized and sufficient follow-up time is needed to determine treatment effect. While case report data represent a large body of data for a rare disease such as AIR, most patients experienced positive treatment outcomes, which may partly be due to the nature of case reports publishing treatment successes.

Despite the variations in study protocol between studies, our work uniquely analyzes all available studies, including case reports, to try to identify which treatments provide the best clinical outcomes. Our study indicates that medications to treat AIR likely have unique properties in treating different symptoms and subtypes. The variability in response to treatment may depend on the duration of the disease or the patient's prior medical history. Characterization of the phenotypes of npAIR and CAR may further help to determine treatment protocols. Additionally, rigorous studies evaluating the ability of imaging modalities such as OCT, wide-field OCT, and wide-field autofluorescence to follow-up disease progression or stabilization while on treatment are needed. The development of a treatment protocol can also utilize inspiration from other difficult to treat autoimmune diseases, such as autoimmune encephalitis, for which treatment is based on principles of pathogenic antibody depletion and personalizing treatment by patient presentation and comorbidities.[63]

Our study highlights the lack of randomized controlled investigations. This statement is corroborated by a 2016 survey of uveitis specialists, which concluded there exists adequate balance to warrant randomized, placebo-controlled trials to determine whether patients with npAIR would benefit from immunomodulatory therapy.[11] Additional studies, such as large-scale, multicenter, and prospective trials, are warranted to assess the impact of systemic and local immunosuppression, and biologic agents, and to aid in the formulation of treatment paradigm while taking into consideration medication adverse effects.

Footnotes and Disclosures

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[1] Drexel University College of Medicine, Philadelphia, Pennsylvania.

[2] Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana.

[3] Department of Ophthalmology, Duke University, Durham, North Carolina.

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Author Contributions:

Conception and design: Kapoor, Sarvepalli, Hadziahmetovic

Data collection: Kapoor, Sarvepalli, Hadziahmetovic

Analysis and interpretation: Kapoor, Sarvepalli, Grewal, Hadziahmetovic

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Abbreviations and Acronyms:
AIR = autoimmune retinopathy; **CAR** = cancer-associated retinopathy; **CME** = cystoid macular edema; **CRT** = central retinal thickness; **ERG** = electroretinogram; **EZ** = ellipsoid zone; **IL-6** = interleukin-6; **IVIG** = intravenous immunoglobulin; **MAR** = melanoma-associated retinopathy; **npAIR** = nonparaneoplastic retinopathy; **RR** = risk ratio; **VA** = visual acuity; **VF** = visual field.

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Correspondence:
Majda Hadziahmetovic, MD, Associate Professor of Ophthalmology, Department of Ophthalmology, Duke University Medical Center, 2351 Erwin Rd, Durham, NC 27710. E-mail: majda.hadziahmetovic@duke.edu.

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