HHS Public Access

Author manuscript

Ophthalmic Genet. Author manuscript; available in PMC 2020 August 08.

Published in final edited form as:

Ophthalmic Genet. 2019 August ; 40(4): 293–297. doi:10.1080/13816810.2019.1650072.

Non-Paraneoplastic Related Retinopathy: clinical challenges and review.

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Abstract

Autoimmune retinopathy (AIR) is a rare inflammatory condition characterized by progressive visual loss, abnormalities in visual fields and electroretinographic exams, along with presence of circulating anti-retinal antibodies. There are two main forms of AIR: paraneoplastic AIR (pAIR) and presumed non-paraneoplastic AIR (npAIR). NpAIR is considered a diagnosis of exclusion, since it is typically made after other causes of retinopathy have been investigated and the absence of malignancy is confirmed. Work-up of a npAIR case is challenging since there are no standartizaded protocols for diagnosis and treatment. The treatment regimen may vary from case to case, and it can be best guided by a set of parameters including electrophysiological responses, visual outcomes, and presence of anti-retinal antibodies. The purpose of this review is to summarize the principal clinical features, investigation, and management of npAIR.

Keywords

anti-retinal antibodies; autoimmune retinopathy; immunosuppressant; retinal antigens; treatment

1. INTRODUCTION

Autoimmune retinopathy (AIR) is a rare inflammatory condition caused by serum autoantibodies that are cross-reactive with retinal and retinal-like antigens, also known as anti-retinal antibodies (ARAs).[1] There are two main forms of AIR: paraneoplastic AIR (pAIR) and presumed non-paraneoplastic AIR (npAIR).[2] In the pAIR category, there are

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Financial and competing interests disclosure: *The authors declare no conflicts of interest.*

cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). NpAIR can be considered a diagnosis of exclusion, because it is typically made after other causes of retinopathy have been investigated and the absence of malignancy confirmed.

The first case report of paraneoplastic AIR (specifically, cancer-associated retinopathy) was published in 1976 by Sawyer et al.[3], but the term “paraneoplastic retinopathy” was coined to describe malignancy-associated AIRs by Klingele et al. later in 1984.[4] In 1987, Thirkill et al. suggested a relationship between CAR and a 23-kDa band on western blot which was later revealed to be recoverin.[5] In 1988, the first case of MAR in a patient with a cutaneous melanoma and night blindness was reported by Berson and Lessl.[6] In 1997, the first case of npAIR was described and its clinical similarity to CAR was noted.[7]

Although the condition has been known for the past four decades, AIR is still challenging to diagnose and treat. It is important to appropriately suspect the disease based on clinical evidence, because it can lead to irreversible blindness.[8]

2. EPIDEMIOLOGY AND CLINICAL FEATURES

Since there are no population-based epidemiological data on AIR in the literature, the prevalence of AIR is currently unknown. AIR diseases are assumed to be rare, with nPAIR constituting less than 1% of cases seen at our tertiary uveitis clinic.[9] Underestimation of the prevalence of AIR could be due to the fact that AIR shares clinical features with other retinal degenerations. npAIR is probably more common than pAIR. CAR is more common than MAR, though the prevalence of MAR is increasing, while the prevalence of CAR is decreasing.[7]

In a large case series of 141 npAIR patients, the mean age at presentation was reported to be 55.9 years, which is younger than the reported mean age at presentation for MAR and CAR patients. In another case series, the mean age at diagnosis for CAR and MAR patients ranging from 24–85 years old was reported to be 65 years.[10] npAIR is more prevalent in females (63–66%) and is associated with a family history of autoimmune disease.[11,12]

Although there is no uniform set of ARAs which circulate in all AIR patients, the many forms have common clinical features. ARAs affect the health and function of retinal cells (e.g. bipolar cells, cones, and rods) in both pAIR and npAIR. Depending on the retinal proteins targeted by ARAs, cell types in AIR patients will be affected to different degrees. Consequently, signs and symptoms can differ depending on which retinal cells are affected.[13]

Symptoms and ocular findings can be asymmetric between eyes and also nonspecific, overlapping with other entities. NpAIR patients usually have a family history of autoimmune disease and the majority do not have previous history of visual disorders but they present with sudden photopsia, night blindness, visual field loss, scotomata, diminished central vision and loss of contrast sensitivity.[14]

Non-paraneoplastic autoimmune retinopathy affects cones, rods or both, CAR affects both rods and cones, and MAR typically affects bipolar cells and rods. Thus, photosensitivity,

loss of color vision, hemeralopia and decreased visual acuity and central vision can be attributed to cone dysfunction, while symptoms like nyctalopia, prolonged dark adaptation, and peripheral field loss can be attributed to rod dysfunction.[15]

At presentation, the fundus can appear normal, including relatively preserved central vision with minimal or no signs of ocular inflammation. Over time, however, fundus changes such as retinal epithelial abnormalities, vascular attenuation and nerve pallor may develop.[8,14–17]

There are no known pathognomonic electrophysiological features for AIR, and generally, there is not much literature about the electrophysiological findings in AIR patients.[16,18] As a result, it is thought that electrophysiological features of AIR are heterogeneous. Electroretinogram (ERG) is an important auxiliary test to identify, quantify and monitor retinal dysfunction because it produces objective data. For AIR patients, the full-field ERGs show abnormal results which depend on the predominance of cone, rod and other neural elements dysfunctioning. Generally, most patients present with greater rod than cone dysfunction, and as the disease progresses over time, the ERG recording becomes extinguished in most patients. The deterioration of visual outcomes and ERG results tend to be more rapid in AIR than in retinal degenerative diseases; patients with retinitis pigmentosa show a slow mean decrease of 10% per year on 30 Hz flicker ERG response.[13]

There are typically significant electroretinographic changes and a rapid onset of symptoms for CAR and MAR, whereas symptoms are slower to progress and electroretinographic changes are slower to manifest for npAIR.[8]

Auxiliary tests can be useful for diagnosing AIR. Visual field testing shows constriction and paracentral or central scotomas. Fluorescein angiography rarely shows leakage in the macula. OCT can show cystoid macular edema, typically in the form of cystic spaces[9] and thinning of the inner retinal layers.[15] Pepple et al. described autofluorescence (AF) and OCT abnormalities in AIR patients such a hyper-AF surrounding a parafoveal region of normal AF which corresponds to the loss of outer retinal complex components as revealed by SD-OCT.[19]

3. DIAGNOSIS

Autoimmune retinopathy is one of the most difficult ophthalmic diagnoses to establish as there is no standard diagnosis consensus, no definitive test available, and in some cases at the onset of disease, patients have normal findings on fundus examination. A patient with no apparent cause for visual dysfunction, an abnormal ERG, and serum ARAs should be highly suspected of having AIR[13]. All patients with suspected AIR but with no past medical history of cancer need to be investigated for occult malignancy before a diagnosis of npAIR can be considered. The work up can be done by assistance of a primary care physician or internist. The investigation should include an extensive interrogatory of patient’s history and system, complete physical exam, laboratory investigation, and imaging such as mammography, CT of the abdomen, pelvis, and chest, brain MRI, colonoscopy or endoscopy.

The differential diagnosis includes other causes of retinal dysfunction or retinal degeneration such as white-dot syndrome spectrum disorders, mainly acute zonal occult outer retinopathy

(AZOOR), inherited retinal diseases particularly retinitis pigmentosa and cone-rod dystrophy, and retinal toxicities secondary of chemotherapy agents and vitamin A deficiency. The ophthalmic work-up should be complemented with fundus autofluorescence, perimetry, and angiography to help rule out other causes of retinopathy.

Retinal autoantibodies have been known to target many retinal antigens in AIR patients. There are various techniques available to investigate the presence of serum autoantibodies against retinal antigens such as immunohistochemistry, Western blotting, ELISA, cytotoxicity assays and multiplex assays. The presence of serum autoantibodies contributes to an AIR diagnosis, but they should not be used in isolation to confirm the diagnosis. Not all patients with a clinical phenotype of MAR, CAR and npAIR have detectable autoantibodies.[20] On the other hand, some healthy subjects may occasionally have antibodies even without retinopathy. For example, Shimazaki et al reported that 62% of normal serum samples had anti-retinal antibody activity as detected by Western blot.[21] In a case series of 193 patients, there was a higher incidence of anti-retinal autoantibodies present in patients diagnosed with cancer (63.5%) than in patients with retinopathy without cancer (41.1%).[11]

Anti-retinal antibodies have been found in other retinal and systemic diseases, and in patients with cancer but without visual symptoms.[22,23] With regard to uveitis, antibodies against outer segments of photoreceptors and Müller cells have been identified in some patients with Vogt-Koyanagi-Harada, sympathetic ophthalmia and Behçet's desease[4], and anti-photoreceptor antibodies have also been identified in significantly more patients with Toxoplasma retinochoroiditis than in controls.[24] There is also data reporting anti-retinal antibodies related to degenerative ocular diseases including both dry and exudative age-related macular degeneration.[25–27] Heckenlively et al. reported the presence of antibodies against retinal proteins in the range of 23 of 26 kDa in 10% of patients with retinitis pigmentosa.[28] In a case series of 30 retinitis pigmentosa patients with cystoid macular edema, antiretinal antibodies were found in 90% of cases.[29]

3.1 ANTI-RETINAL ANTIBODIES

So far, at least 17 different kinds of anti-retinal antibodies have been found in patients presumed to have AIR, and some of them may be present in more than one specific disease. [20] npAIR's most common anti-retinal antibodies are against recoverin (23 kDa), α-enolase (46kDa), rod transducin-α (38kDa), Carbonic Anhydrase II (30kDa), the inner retinal layer (35-kDa antibody against retinal Müller cell–associated antigen), arrestin (48kDa), interphotoreceptor-binding protein (141kDa) and unidentified antigen targets (22, 34, 35, 37, 40, 68 kDa).[1,20]

Recoverin is a 23-kDa calcium-binding protein localized in photoreceptors, and although it is most usually specific for CAR, it can also be related to npAIR.[7,29,30] This protein is involved in regulating rhodopsin phosphorylation during dark and light adaptation via a calcium-dependent process. Anti-recoverin retinopathy has been associated with various cancers including small-cell lung, uterine sarcoma, cervical and endometrial carcinomas, invasive thymoma, and mixed Mullerian tumors. The clinical phenotype of anti-recoverin-associated CAR is usually aggressive, with severe dysfunction of both rods and cones and

significant vision loss.[31] In some cases, patients cannot perceive light at all. Adamus et al. demonstrated that peritoneal injection of rat models with recoverin caused photoreceptor cell degeneration and the formation of features associated with uveoretinitis such as photoreceptor cell layer loss, perivasculitis, vitreous cells, and retinal lesions.[32]

a-Enolase is a 46-kDa protein found in tumor tissue and in the cell membranes and cytoplasm of normal tissue (e.g. Muller cells, rods, cones, and retinal ganglion cells).[1] CAR secondary to autoantibodies against a-enolase, was reported in patients months to years after the development of lung, breast, prostate, uterine, bladder, salivary gland, and gastro-intestinal tract carcinomas and chronic lymphocytic leukemia.[33,34] Anti-enolase antibodies have also been described in npAIR patients and have been found in 10% of healthy subjects and related to systemic autoimmune diseases such as lupus erythematosus, Behçet disease, inflammatory bowel disease, primary sclerosing cholangitis, mixed cryoglobinemia, systemic sclerosis, and multiple sclerosis.[17,20]

Transducin, also known as G-protein, is a 3-subunit guanine nucleotide-binding protein that stimulates the coupling of cGMP-phosphodiesterase to cGMP in the photo-transduction cascade leading to hyperpolarization of the photoreceptor. Transducins have three protein subunits, α, β, and γ. In rods and cones, the transducin α -subunits are encoded by separate genes: GNAT1 in rods and GNAT2 in cones.[20] When transducin-α is inactivated by autoantibodies, there may be a reduction in photoreceptor signaling as well as changes in apoptosis and intracellular calcium levels.[31]

4. MANAGEMENT

There is currently no standardized treatment protocol for AIR. However, since AIR is a systemic disease and presumed to be autoimmune, immunomodulatory therapy such as local or systemic corticosteroids, intravenous immunoglobulins, plasmapheresis, and systemic immunosuppression are often offered as a treatment strategies.[17] There is limited literature on immunomodulatory strategies based on retrospective case reports and case series. In most cases, treatments are reported based on subjective interpretations and some studies have been controversial in regards to treatment response.[10,11,30,35] Some specialists try a short-term treatment that can be done with intravitreal triamcinolone or sub-tenon Depomedrol. Such drugs help confirm the diagnosis before starting systemic long term immunosuppression, which can cause adverse effects and usually lasts over a year.[14] Immunosuppression therapy can be done with corticosteroids and immunomodulatory drugs such as mycophenolate mofetil, azathioprine, intravenous immunoglobulin, cyclosporine and infliximab.[16]

Ferreyra et al. conducted a retrospective review of 30 AIR patients treated with immunosuppression (local and systemic), including cases of CAR, npAIR, and npAIR with cystoid macular edema. There was improvement in 54% (7 of 13) of npAIR patients and 73% (8 of 11) in npAIR/CME patients. Those who did not respond to immunosuppression therapy (nonresponders) were also less tolerant to systemic immunosuppression because 56% (5 of 9) of nonresponders had adverse effects and stopped the use of at least 1 systemic immunosuppressive medication, while this only happened in 25% (5 of 20) of responders.[14]

Although this study had some limitations (e.g. retrospective review), each patient had individualized immunosuppression therapy, and thus, the researchers were able to analyze heterogeneous treatments and variable patient follow-up.

Davoudi et al. published a retrospective case series of 16 AIR patients (1 MAR, 6 CAR and 9 npAIR subjects) who were treated with Rituximab. OCT and ERG parameters remained stable during treatment and six months after rituximab initiation, 77% of eyes had stable or improved visual acuity. Most patients, however, took a concomitant immunosuppressive medication with rituximab and had regimens that varied over time.[36]

Two other case reports published that npAIR patients responded well to rituximab, with overall improvements in retinal function.[37,38] Maleki et al. conducted a case series for six npAIR patients who received rituximab and/or combination therapy. Out of all the patients, they found that visual acuity was stable in 66.7%, 50% showed stability in visual field testing, 33.3% showed stability or improvement in ERG, and at least one pathogenically proven ARA band resolved after treatment. Boudreault et al. performed a retrospective visual function analysis of four npAIR cases and concluded that rituximab infusion may stabilize the evolution of retinal dysfunction in npAIR patients that are not responsive to other immunosuppression treatments[13]

Periodic reevaluation of ARAs following treatment has been useful in monitoring the therapeutic response of AIR patients. However, the clinical significance of this finding is unclear.[1] Titers of ARAs have previously been shown to decline in response to therapy,[20] but this outcome is controversial and not well described.[39] It is advisable to interpret antibody test results in combination with other retinal and visual function parameters including visual acuity, visual fields tests, ffERG and multi-modal imaging in order to develop the best treatment for AIR patients.

5. CONCLUSION

Currently, besides advances in understanding the clinical aspects and pathophysiology of AIR, there are still no standard diagnostics, laboratory and management guidelines for this disease. As discussed above, some cases may be difficult to identify, which can delay the diagnosis and lead to a worsening prognosis. One challenge is that AIR does not have a pattern of presentation and evolution, because patients often present with different combinations of anti-retinal antibodies. The specific roles of ARAs in AIR pathophysiology also remain unclear. There are many questions about which antibodies are pathogenic and/or benign, and further studies are needed to elucidate what triggers would result in autoimmune attacks on retinal cells. Additionally, more prospective, randomized controlled trials would allow us to better understand the nature and underlying pathophysiology of AIR.

Acknowledgements:

The Jonas Children’s Vision Care and Bernard & Shirlee Brown Glaucoma Laboratory are supported by the National Institutes of Health [P30EY019007, R01EY018213, R01EY024698, R01EY026682, R21AG050437], National Cancer Institute Core [5P30CA013696], Foundation Fighting Blindness [TA-NMT-0116–0692-COLU], the Research to Prevent Blindness (RPB) Physician-Scientist Award, and unrestricted funds from RPB, New York, NY, USA. S.H.T. is a member of the RD-CURE Consortium and is supported by Kobi and Nancy Karp, the

Crowley Family Fund, the Rosenbaum Family Foundation, the Tistou and Charlotte Kerstan Foundation, the Schneeweiss Stem Cell Fund, New York State [C029572], and the Gebroe Family Foundation.

6. REFERENCES

1. Comlekoglu DU, Thompson IA, Sen HN. Autoimmune retinopathy. Curr Opin Ophthalmol. 2013;24(6):598–605. doi:10.1097/ICU.0b013e3283654e1e. [PubMed: 24100366]
2. Fox AR, Gordon LK, Heckenlively JR, et al. Consensus on the Diagnosis and Management of Nonparaneoplastic Autoimmune Retinopathy Using a Modified Delphi Approach. Am J Ophthalmol. 2016; 168:183–190 doi:10.1016/j.ajo.2016.05.013. [PubMed: 27210277]
3. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF. Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol. 1976; 81(5):606–13. doi: 10.1016/0002-9394(76)90125-2. [PubMed: 179323]
4. Chan CC, Palestine AG, Nussenblatt RB, Roberge FG BD. Anti-retinal auto-antibodies in Vogt-Koyanagi-Harada Syndrome, Behcet's Disease and Sympathetic Ophthalmia. Ophthalmology. 1985;92(8):1025–1028. 10.1016/S0161-6420(85)33911-8. [PubMed: 3900848]
5. Thirkill CE, Roth AM KJ. Cancer-Associated Retinopathy. Arch Ophthalmol. 1987;105(3):372–375. doi:10.1001/archopht.1987.01060030092033. [PubMed: 2950846]
6. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. Am J Ophthalmol. 1988;106(15):307–311. doi:10.1016/0002-9394(88)90366-2. [PubMed: 2971322]
7. Mizener JB, Kimura AE, Adamus G, Thirkill CE, Goeken JA, Kardon RH. Autoimmune retinopathy in the absence of cancer. Am J Ophthalmol. 1997;123(5):607–618. doi:10.1016/S0002-9394(14)71073-6. [PubMed: 9152066]
8. Sobrin L Progress Toward Precisely Diagnosing Autoimmune Retinopathy. Am J Ophthalmol. 2018:3–4. doi:10.1016/j.ajo.2018.01.002. [PubMed: 29100588]
9. Grange L, Dalal M, Nussemblat RB SN. Autoimmune Retinopathy. Am J Ophthalmol. 2014;157(2): 266–272. doi: 10.1016/j.ajo.2013.09.019. [PubMed: 24315290]
10. Braithwaite T, Vugler A, ARO Tufail A 2012;228:131–142. Autoimmune retinopathy. Ophthalmologica. 2012;(228):131–142. doi:10.1097/ICU.0b013e3283654e1e. [PubMed: 22846442]
11. Ferreyra HA, Jayasundera T, Khan NW, He S, Lu Y, Heckenlively JR. Management of autoimmune retinopathies with immunosuppression. Arch Ophthalmol. 2009;127(4):390–397. doi:10.1001/archophthalmol.2009.24. [PubMed: 19365013]
12. Adamus G, Ren G, Weleber RG. Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy. BMC Ophthalmol. 2004;4:1–9. doi:10.1186/1471-2415-4-5. [PubMed: 15018630]
13. Boudreault K, Justus S, Sengillo JD, et al. Efficacy of rituximab in non-paraneoplastic autoimmune retinopathy. Orphanet J Rare Dis. 2017;12(1):1–15. doi:10.1186/s13023-017-0680-7. [PubMed: 28057032]
14. Heckenlively JR, Ferreyra HA. Autoimmune retinopathy: A review and summary. Semin Immunopathol. 2008;30(2):127–134. doi:10.1007/s00281-008-0114-7. [PubMed: 18408929]
15. Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: Evaluation and management. Surv Ophthalmol. 2013;58(5):430–458. doi:10.1016/j.survophthal.2012.09.001. [PubMed: 23969019]
16. Canamary AM, Takahashi WY, Sallum JMF. Autoimmune retinopathy: A Review. Int J Retin Vitr. 2018;4(1):1. doi:10.1186/s40942-017-0104-9.
17. Forooghian F, Cao S, Cui J, Joanne A. The Enigma of Autoimmune Retinopathy AIR : Clinical Features CIHR Author Manuscript Antiretinal Antibodies : Pathogenic Uncertainties. 2016;55(2). doi:10.1097/IIO.0000000000000063.
18. Matsui Y, Mehta MC, Katsumi O, Brodie SE, Hirose T. Electrophysiological findings in paraneoplastic retinopathy. Graefe's Arch Clin Exp Ophthalmol. 1992;230(4):324–328. doi: 10.1007/BF00165939. [PubMed: 1505762]

19. Pepple KL, Cusick M, Jaffe GJ, Mruthyunjaya P. SD-OCT and autofluorescence characteristics of autoimmune retinopathy. Br J Ophthalmol. 2013;97(2):139–144. doi:10.1136/bjophthalmol-2012-302524. [PubMed: 23221966]
20. Grewal DS, Fishman GA, Jampol LM. Autoimmune Retinopathy and Antiretinal Antibodies: a Review. Retina. 2014;34(5):827–845. doi:10.1097/IAE.0000000000000119. [PubMed: 24646664]
21. Shimazaki K, Jirawuthiworavong GV., Heckenlively JR, Gordon LK. Frequency of anti-retinal antibodies in normal human serum. J Neuro-Ophthalmology. 2008;28(1):5–11. doi:10.1097/WNO.0b013e318167549f.
22. Bazhin a V, Shifrina ON, Savchenko MS, et al. Low titre autoantibodies against recoverin in sera of patients with small cell lung cancer but without a loss of vision. Lung Cancer. 2001; 34(1):99–104 doi:S0169500201002124 [pii]. [PubMed: 11557119]
23. Savchenko MS, Bazhin AV., Shifrina ON, et al. Antirecoverin autoantibodies in the patient with non-small cell lung cancer but without cancer-associated retinopathy. Lung Cancer. 2003;41(3):363–367. doi:10.1016/S0169-5002(03)00239-3. [PubMed: 12928127]
24. Whittle RM, Wallace GR, Whiston RA, Dumonde DC, Stanford MR. Human antiretinal antibodies in toxoplasma retinochoroiditis. Br J Ophthalmol. 1998;82(9):1017–1021. doi:10.1136/bjo.82.9.1017. [PubMed: 9893591]
25. Patel N, Ohbayashi M, Nugent AK, et al. Circulating anti-retinal antibodies as immune markers in age-related macular degeneration. Immunology. 2005;115(3):422–30 doi:10.1111/j.1365-2567.2005.02173.x. [PubMed: 15946260]
26. Penfold PL, Madigan MC, Gillies MC, Provis JM. Immunological and aetiological aspects of macular degeneration. Prog Retin Eye Res. 2001;20(3):385–414 doi:10.1016/S1350-9462(00)00025-2. [PubMed: 11286898]
27. Chen H, Wu L, Pan S, Wu DZ. An immunologic study on age-related macular degeneration. Eye Sci. 1993;9(3):113–120. http://www.ncbi.nlm.nih.gov/pubmed/8168604.
28. Heckenlively JR, Fawzi AA, Oversier J, Jordan BL, Aptsiauri N. Autoimmune retinopathy: Patients with antirecoverin immunoreactivity and panretinal degeneration. Arch Ophthalmol. 2000;118(11):1525–33 doi:10.1001/archopht.118.11.1525. [PubMed: 11074809]
29. Heckenlively JR, Jordan BL, Aptsiauri N. Association of Antiretinal Antibodies and Cystoid Macular Edema in Patients With Retinitis Pigmentosa. 1999;127(5):565–73.
30. Whitcup SM, Vistica BP, Milam AH, Nussenblatt RB, Gery I. Recoverin-associated retinopathy: A clinically and immunologically distinctive disease. Am J Ophthalmol. 1998; 126(2):230–7 doi:10.1016/S0002-9394(98)00149-4. [PubMed: 9727517]
31. Adamus G, Brown L, Weleber RG. Molecular biomarkers for autoimmune retinopathies: Significance of anti-transducin-alpha autoantibodies. Exp Mol Pathol. 2009;87(3):195–203. doi:10.1016/j.yexmp.2009.08.003. [PubMed: 19744478]
32. Adamus G, Ortega H, Witkowska D, Polans A. Recoverin: a Potent Uveitogen for the Induction of Photoreceptor Degeneration in Lewis Rats. Exp Eye Res. 1994;59(4):447–456. doi:10.1006/exer.1994.1130. [PubMed: 7859820]
33. Adamus G, Aptsiauri N, Guy J, Heckenlively J, Flannery J, Hargrave PA. The occurrence of serum autoantibodies against enolase in cancer-associated retinopathy. Clin Immunol Immunopathol. 1996;78(2):120–9 doi:10.1006/clin.1996.0021. [PubMed: 8625554]
34. Adamus G, Amundson D, Seigel GM, MacHnicki M. Anti-enolase-α autoantibodies in cancer-associated retinopathy: Epitope mapping and cytotoxicity on retinal cells. J Autoimmun. 1998;11(6):671–7 doi:10.1006/jaut.1998.0239. [PubMed: 9878089]
35. Weleber RG, Watzke RC, Shults WT, et al. Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies. Am J Ophthalmol. 2005;139(5):780–94 doi:10.1016/j.ajo.2004.12.104. [PubMed: 15860281]
36. Davoudi S, Ebrahimiadib N, Yasa C, et al. Outcomes in Autoimmune Retinopathy Patients Treated With Rituximab. Am J Ophthalmol. 2017;180:124–132. doi:10.1016/j.ajo.2017.04.019. [PubMed: 28483493]
37. Uludag G, Onal S, Arf S, et al. Electroretinographic improvement after rituximab therapy in a patient with autoimmune retinopathy. Am J Ophthalmol Case Reports. 2016;2:4–7. doi:10.1016/j.ajoc.2016.03.007.

38. Fox A, Jeffrey B, Hasni S, Nussenblatt R, Sen HN. Rituximab treatment for nonparaneoplastic autoimmune retinopathy. Can J Ophthalmol. 2015;50(6):e101–e104. doi:10.1016/j.jcjo.2015.08.009. [PubMed: 26651312]

39. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: A phase I/II dose-escalation trial of rituximab. Arthritis Rheum. 2004; 50(8):2580–9 doi:10.1002/art.20430. [PubMed: 15334472]