Int Ophthalmol Clin. Author manuscript; available in PMC 2016 July 12.

Published in final edited form as:
Int Ophthalmol Clin. 2015 ; 55(2): 81–91. doi:10.1097/IIO.0000000000000063.

The Enigma of Autoimmune Retinopathy

Farzin Forooghian, MD, MSc, FRCSC[*], **Sijia Cao, MD**[*], **Jing Cui, MD**[*], and **Joanne A. Matsubara, PhD**[**]

[*]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Introduction

Autoimmune retinopathy (AIR) refers to an immunologic process whereby retinal antigens are aberrantly recognized as autoantigens, leading to retinal degeneration. AIR was initially described in 1976 as a paraneoplastic syndrome, termed cancer-associated retinopathy (CAR), secondary to a remote malignancy.[1] Laboratory investigations revealed that the serum of patients with CAR contained autoantibodies against the photoreceptor protein recoverin, which are believed to represent the underlying etiology of CAR.[2,3] A related syndrome, termed melanoma-associated retinopathy (MAR), was reported in patients with cutaneous malignant melanoma who were found to have autoantibodies to an unknown antigen on bipolar cells.[4,5] Since that time, AIR in the absence of neoplasm, termed nonparaneoplastic AIR (npAIR), has been described as well.[6] Along with this has come the identification of several novel putative antiretinal autoantibodies. Although all these novel discoveries have expanded our knowledge of AIR, they have also brought with them some confusion. There are numerous excellent reviews of AIR that have recently been published in the literature.[7–13] The purpose of this current article is not to provide another review of this topic, but rather to highlight some of the ambiguity and uncertainty that exists in this field. For the purposes of this review, the term AIR will be used to refer to CAR, npAIR, and MAR, as the ocular features and proposed pathogenesis of these entities are essentially the same.

AIR: Clinical Features

The clinical diagnosis of AIR can be challenging, as the symptoms and signs can be nonspecific and often overlap with those of other entities. Symptoms are diverse and can include subacute vision loss, diminished central vision, loss of contrast sensitivity, scotomas, photopsia, nyctalopia, photoaversion, and/or dyschromatopsia.[10,13] Symptoms are usually bilateral, but can be asymmetric. On clinical examination, the fundus can appear normal initially. Later in the course of the disease, patients may develop fundus changes such as retinal pigment epithelial abnormalities (eg, bone spicules), vascular attenuation, and/or nerve pallor. Usually, minimal or no signs of intraocular inflammation are seen.[10] A female

[**]Correspondence to: Dr Joanne A Matsubara, Department of Ophthalmology and Visual Sciences, Eye Care Centre, 2550 Willow Street, Vancouver, BC, Canada V5Z 3N9; jms@mail.ubc.ca.

The authors declare that they have no conflicts of interest to disclose.

predominance has been described, as well as a family history of autoimmune disease.[14,15] The mean age of onset has been described in the range of 55 to 65 years, with npAIR having a younger age of onset than CAR and MAR.[15–17] Cystoid macular edema has also been described in AIR.[14] Ancillary studies that can be useful in the diagnosis of AIR include visual field (VF) testing, electroretinography (ERG), fundus autofluorescence (FAF) imaging, and optical coherence tomography (OCT). VF testing can show constriction of VF, whereas ERG can show reduced responses, but there are no VF or ERG features that are pathognomonic for AIR.[10,11] An "electronegative" ERG has been reported in many cases of AIR, but this finding is nonspecific and has also been described in inherited retinal degenerations (eg, congenital stationary night blindness) and inflammatory eye disease (eg, birdshot chorioretinopathy).[11,13,18,19] FAF imaging and OCT in AIR have shown a hyperautofluorescent ring in the parafoveal region, with corresponding attenuation of the photoreceptor layer from the region of the hyperautofluorescent ring toward the retinal periphery.[20–22] Many authors feel that the diagnosis of AIR is supported by the presence of circulating antiretinal antibodies.[12,14,23] The overall prevalence of AIR is not known, due to a lack of population-based epidemiological data, although it has been estimated to represent far less than 1% of cases seen at a tertiary ocular immunology and uveitis clinic.[10,12]

Various authors have proposed diagnostic criteria for AIR.[10,12–14] However, there is no international consensus on these diagnostic criteria, and as a result the clinical features of AIR can vary considerably between different groups of clinicians.[10] International consensus has been reached on diagnostic criteria for other immune-mediated ocular diseases such as ocular sarcoidosis.[23] Similar international consensus and standardization would be useful for AIR.

Antiretinal Antibodies: Pathogenic Uncertainties

Many authors believe that the presence of antiretinal antibodies is required for the diagnosis of AIR.[10,12–14,23] Autoantibodies can be seen in both healthy and diseased patients. In healthy patients, they are likely simply an epiphenomenon without any pathogenic potential. Antiretinal antibodies have been described in a variety of systemic autoimmune diseases such as Behcet disease, inflammatory bowel disease, systemic lupus erythrematosis (SLE), and multiple sclerosis,[24–27] as well as degenerative ocular diseases such as age-related macular degeneration, [28] and both infectious and noninfectious uveitis.[29,30] Antiretinal antibodies have been reported in up to 42% of normal controls.[31] Proving the pathogenicity of these autoantibodies in various disease states is difficult, and requires rigorous scientific proof. A recent review has shown that to date there have been at least 17 different antiretinal antibodies described in patients with presumed AIR.[7] Given these observations, it is crucial for clinicians to know which of these retinal autoantibodies are truly pathogenic and which are not.

The pathogenicity of some antiretinal antibodies has been well established in both in vitro and in vivo scientific experimentation. However, the pathogenicity of other retinal autoantibodies has not been so well studied. Using Western blot techniques, Shimazaki et al[32] have shown that 33% of normal human serum demonstrates 1 to 2 bands, and 22% of normal human serum contains ≥5 bands. Given the numerous putative retinal autoantibodies

that have been described, and the fact that normal serum can have significant antiretinal antibody activity, it is of paramount importance to definitively prove the pathogenicity of the autoantibodies suspected of causing AIR. Several authors have raised concerns over the uncertainty of pathogenicity of antiretinal antibodies.[7–11,33]

Autoantibodies against recoverin, a photoreceptor-specific calcium-binding protein, have a well-established role in pathogenicity of immune-mediated retinal degeneration. Both cell culture experiments and animal models have shown that, following internalization into the cell, anti-recoverin antibodies induce apoptotic cell death mediated by caspase-dependent pathways along with intracellular calcium influx.[34–39] Both in vitro and in vivo studies have also demonstrated the retinal toxicity of autoantibodies against α-enolase through similar caspase-dependent apoptotic mechanisms.[40–42] Autoantibodies targeting various other retinal proteins have also been implicated as putative causative agents based on the identification of these antibodies in the serum of patients with presumed AIR. These include antibodies against carbonic anhydrase II (which is abundant in ocular tissues)[17,43,44] and the retina-specific tubby-like protein 1 (TULP1).[45] The mere presence of autoantibodies in patient sera does not imply pathogenicity, as the antibodies could represent either “the secondary consequence of tissue damage, or the harmless footprint of an etiologic agent.”[44] Ultimately, basic science experimentation is needed to prove pathogenicity of these autoantibodies. In the case of autoantibodies targeting carbonic anhydrase II, basic science data suggesting pathogenicity is limited to cell culture studies.[46] There are no published reports of basic science studies evaluating the potential retinal toxicity of anti-TULP1 antibodies. Given the uncertainties that exist in the field of AIR with respect to pathogenicity of antiretinal antibodies, definitive scientific proof, including animal studies, are needed to explore the pathogenic potential (if any) of these antibodies.

Whereas the case for retinal pathogenicity of autoantibodies against photoreceptor-specific proteins such as recoverin is intuitive and strongly supported by basic science and clinical research, the case for other autoantibodies that target ubiquitously expressed proteins is less clear. Autoantibodies against the ubiquitous glycolytic enzymes α-enolase, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and aldolase have been implicated in the pathogenesis of AIR in several reports.[43,47–50] However, other systemic autoimmune phenomena have not consistently been described in association with these autoantibodies. If these antiretinal antibodies are truly pathogenic, then it is unclear why their toxicity would be specific to the retina when their targets are ubiquitous. Cell culture studies have suggested that anti-α-enolase antibodies from patients with CAR recognize specific epitopes that are not recognized by anti-α-enolase antibodies from healthy patients.[42] However, this still does not adequately explain why the toxicity of anti-α-enolase antibodies should be limited to the retina, as α-enolase is ubiquitous in humans.[51] It is possible that these autoantibodies are simply an epiphenomenon, and are indeed not pathogenic. It has been observed that 11% of healthy patients have autoantibodies against α-enolase.[25] Autoantibodies against α-enolase have been described in patients with a wide variety of systemic autoimmune diseases, including SLE, Behcet disease, inflammatory bowel disease, primary sclerosing cholangitis, mixed cryoglobinemia, systemic sclerosis, and multiple sclerosis.[25–27,51,52] In SLE, it has been shown that they do not correlate with any clinical or serological disease parameter.[53] In various other autoimmune diseases where α-enolase autoantibodies are found, there has

been no clear demonstration of their pathogenicity.[51] These observations raise some doubts about the pathogenic role of anti-α-enolase antibodies in AIR.

Another class of ubiquitous proteins that have been implicated in AIR based on autoantibody detection in patient sera are heat shock proteins.[54–56] Other autoantibody targets that have been proposed to play a role in AIR include transducin-β, transducin-α, neurofilament protein, photoreceptor cell–specific nuclear receptor, Muller cell–specific antigen, transient receptor potential cation channel, subfamily M, member 1 (TRPM1), and a number of yet unidentified putative antigen targets.[10,11,57] Unfortunately, there are no in vitro or in vivo studies to support the pathogenicity of any of these autoantibodies in AIR. On the basis of these observations, it would seem prudent to conclude that the retinal pathogenic potential of many of the autoantibodies proposed to be involved in AIR remains uncertain.

Laboratory Testing: Lack of Standardization and Validation

Various laboratory techniques, including immunohistochemistry (IHC), Western blot, and enzyme-linked immunosorbent assay (ELISA), have been described for the detection of circulating antiretinal antibodies. Each method has its advantages and disadvantages. IHC involves incubating patient sera with section of normal retina. A secondary antibody (linked to a colorimetric or fluorescent compound) is then used to detect the binding of patient sera to the normal retina sections. IHC will give a measure of the total antiretinal antibody level in patient sera, and is not able to detect antibodies against specific proteins. The amount of patient sera binding to normal retina is often assessed qualitatively, but methods exist for quantification of antiretinal antibody binding. Western blot involves separating retinal extract or pure retinal proteins on a membrane using electrophoresis. The membrane is incubated with patient sera, and then the binding of the patient sera to the proteins on the membrane is detected using a secondary antibody (similar to IHC). When a band is seen on a Western blot against retinal extract suggesting antibodies against a specific protein, then a confirmatory blot needs to be performed using that specific protein. For example, if the Western blot using retinal extract shows a protein band at around 23 kDa, then another blot using purified human recoverin needs to performed to confirm that the patient has anti-recoverin antibodies. The identity of a protein on a blot performed using retinal extract cannot be assumed based on its molecular weight. One study reported that 10% of patients screened had 23 kDa bands on Western blot, but that only 16% of these were actually confirmed to be anti-recoverin when purified recoverin was used on the blot, demonstrating that there is at least 1 other protein at 23kDA that reacts with many patients' sera.[58] ELISA is similar to Western blot in that it can detect antibodies against specific retinal proteins. In this technique, small wells are coated with a specific protein, patient sera is added, and then a secondary antibody is added to detect binding (similar to IHC and Western blot). Regardless of the technique that is being used to detect antiretinal antibodies, it is crucial to incorporate proper controls, including positive controls, negative controls, loading controls, replicates, and standard curves.[7,57] Without stringent controls, antiretinal antibody testing can generate false-positive and false-negative results. The use of proper controls is especially important when performing Western blot as false positives against anti-recoverin and anti-α-enolase, the 2 most common antiretinal antibodies that have been reported in AIR, can occur

if appropriate negative controls are not used.[7,57] Concern over lack of the reporting of proper controls in the antiretinal antibody literature has previously been raised.[10,33,57]

Various laboratories are now offering antiretinal antibody testing as a commercial service.[7] Furthermore, some of these laboratories have obtained Clinical Laboratory Improvement Amendments (CLIA) certification for antiretinal antibody testing.[59] It is important to note that CLIA approval simply refers to the practice of good laboratory techniques and standards, and does not mean that the laboratory test being offered is standardized and validated. The lack of standardization between various laboratories performing antiretinal antibody testing has been shown to result in poor concordance of test results between laboratories.[60] This poor concordance between laboratories that perform antiretinal antibody testing has led some authors to recommend sending patient samples to at least 2 different laboratories when ordering antiretinal antibody testing.[7]

Another aspect of antiretinal antibody testing that is lacking is stringent validation to ensure that laboratory results correlate with clinical disease. This would require determining the sensitivity, specificity, positive predictive value, and negative predictive value of antiretinal antibody testing. These parameters have not yet been established for any antiretinal antibody test.[11] Furthermore, the majority of patients with AIR have several bands detected on Western blot analysis.[13,14] Some of these bands could represent pathogenic antiretinal antibodies, whereas others could be incidental antiretinal antibodies that have no clinical significance. It would be useful to have validated criteria with respect to these bands (number, intensity, molecular weight, and isotype), which can assist clinicians in assessing the clinical meaningfulness of these results. Such criteria could be similar to those used in the diagnosis of Lyme disease using Western blot, where testing (even on healthy patients) often reveals multiple bands. In the setting of Lyme, certain specific bands are required to be present before the diagnosis of Lyme can be made.[61] Unfortunately, these types of validated criteria are currently not available for antiretinal antibody testing.

Treatment Options: Lack of Prospective Randomized Studies

The treatment of AIR has been extensively reviewed in numerous recent review articles.[7–13] Most authors agree that if there is an underlying malignancy, then this should be treated. Because of the presumed autoimmune nature of AIR, treatment strategies have focused on immunomodulatory therapy. Various strategies have included local or systemic corticosteroids, intravenous immunoglobulins, plasmapheresis, and systemic immunosuppresion.[10] Reports using these immunomodulatory strategies have been limited to retrospective case reports and case series. The few small studies that have evaluated the treatment of AIR have reported conflicting results, with some studies reporting improvement with treatment and other reporting worsening despite treatment.[11,14,62,63] The largest study has involved 30 patients treated with immunosuppression (local and systemic), and improvement was reported in 70%of the patient cohort.[14] However, this study was limited by its retrospective nature, lack of predefined treatment regimen with heterogenous treatments, variable patient follow-up, and variable clinical presentations of AIR. Given the proposed antibody-mediated nature of AIR, a therapeutic agent that targets B cells and thus reduces systemic antibody levels would seem reasonable. Rituximab is a monoclonal

antibody that targets B cells, and a few case reports have demonstrated successful treatment of AIR using this agent.[64–66] The difficulty in translating the treatment findings for AIR from the literature lies in the fact that all the literature on this topic is based on retrospective reviews. To date, there have been no prospective, placebo-controlled, and/or randomized studies on the treatment of AIR. Furthermore, there are no good markers available to evaluate treatment effects.[14] Until such data become available, the treatment options for AIR will remain uncertain.

Conclusions

The diagnosis and management of AIR remains a challenge. Various diagnostic criteria for AIR have been proposed,[10,12–14] but to date there is no international consensus on these criteria. Detection of circulating antiretinal antibodies is considered by many authors as an important criterion that needs to be met for the diagnosis of AIR.[10,12–14] However, there is no consensus on which antibodies are pathogenic and which are not pathogenic. Furthermore, there is no consensus on which particular antibodies or combination of antibodies are suggestive of AIR, and which antibodies can be considered normal. For example, a clinical scenario can arise when a patient receives an IHC result that is "positive," or a WB result that shows "bands at 28, 35, and 78 kDa." Given the data that are currently available in the literature, it is extremely difficult for clinicians to know what (if any) clinical meaning these results have. The only antiretinal antibody that has strong evidence for pathogenicity seems to be anti-recoverin. The pathogenic potential of other putative antiretinal antibodies that have been described, including anti-α-enolase, seems equivocal based on the current data in the literature. These other antiretinal antibodies could simply be a consequence of the tissue damage from a primary retinal degeneration, or the "harmless footprint" of an unrelated systemic autoimmune process. There are no randomized controlled trials for the treatment of AIR, and an evidence-based treatment strategy is lacking. Although much has been learned about AIR in the past few years, there are still many uncertainties remaining. Until these ambiguities are resolved, the diagnosis and management of AIR will remain an enigma.

References

1. Sawyer RA, Selhorst JB, Zimmerman LE, et al. Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol. 1976; 81:606–613. [PubMed: 179323]
2. Thirkill CE, Roth AM, Keltner JL. Cancer-associated retinopathy. Arch Ophthalmol. 1987; 105:372–375. [PubMed: 2950846]
3. Thirkill CE, Tait RC, Tyler NK, et al. The cancer-associated retinopathy antigen is a recoverin-like protein. Invest Ophthalmol Vis Sci. 1992; 33:2768–2772. [PubMed: 1388144]
4. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. Am J Ophthalmol. 1988; 106:307–311. [PubMed: 2971322]
5. Milam AH, Saari JC, Jacobson SG, et al. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. Invest Ophthalmol Vis Sci. 1993; 34:91–100. [PubMed: 8425845]
6. Mizener JB, Kimura AE, Adamus G, et al. Autoimmune retinopathy in the absence of cancer. Am J Ophthalmol. 1997; 123:607–618. [PubMed: 9152066]
7. Grewal DS, Fishman GA, Jampol LM. Autoimmune retinopathy and antiretinal antibodies: a review. Retina. 2014; 34:827–845. [PubMed: 24646664]

8. Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: evaluation and management. Surv Ophthalmol. 2013; 58:430–458. [PubMed: 23969019]
9. Braithwaite T, Holder GE, Lee RW, et al. Diagnostic features of the autoimmune retinopathies. Autoimmun Rev. 2014; 13:534–538. [PubMed: 24424196]
10. Grange L, Dalal M, Nussenblatt RB, et al. Autoimmune retinopathy. Am J Ophthalmol. 2014; 157:266e261–272.e261. [PubMed: 24315290]
11. Braithwaite T, Vugler A, Tufail A. Autoimmune retinopathy. Ophthalmologica. 2012; 228:131–142. [PubMed: 22846442]
12. Comlekoglu DU, Thompson IA, Sen HN. Autoimmune retinopathy. Curr Opin Ophthalmol. 2013; 24:598–605. [PubMed: 24100366]
13. Heckenlively JR, Ferreyra HA. Autoimmune retinopathy: a review and summary. Semin Immunopathol. 2008; 30:127–134. [PubMed: 18408929]
14. Ferreyra HA, Jayasundera T, Khan NW, et al. Management of autoimmune retinopathies with immunosuppression. Arch Ophthalmol. 2009; 127:390–397. [PubMed: 19365013]
15. Adamus G, Ren G, Weleber RG. Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy. BMC Ophthalmol. 2004; 4:5. [PubMed: 15180904]
16. Keltner JL, Thirkill CE, Yip PT. Clinical and immunologic characteristics of melanoma-associated retinopathy syndrome: eleven new cases and a review of 51 previously published cases. J Neuroophthalmol. 2001; 21:173–187. [PubMed: 11725182]
17. Adamus G. Autoantibody targets and their cancer relationship in the pathogenicity of paraneoplastic retinopathy. Autoimmun Rev. 2009; 8:410–414. [PubMed: 19168157]
18. Koh AH, Hogg CR, Holder GE. The incidence of negative ERG in clinical practice. Doc Ophthalmol. 2001; 102:19–30. [PubMed: 11475363]
19. Holder GE, Robson AG, Pavesio C, et al. Electrophysiological characterisation and monitoring in the management of birdshot chorioretinopathy. Br J Ophthalmol. 2005; 89:709–718. [PubMed: 15923507]
20. Lima LH, Greenberg JP, Greenstein VC, et al. Hyperautofluorescent ring in autoimmune retinopathy. Retina. 2012; 32:1385–1394. [PubMed: 22218149]
21. Abazari A, Allam SS, Adamus G, et al. Optical coherence tomography findings in autoimmune retinopathy. Am J Ophthalmol. 2012; 153:750e751–756.e751. [PubMed: 22245461]
22. Pepple KL, Cusick M, Jaffe GJ, et al. SD-OCT and autofluorescence characteristics of autoimmune retinopathy. Br J Ophthalmol. 2013; 97:139–144. [PubMed: 23221966]
23. Herbort, CP., Rao, NA., Mochizuki, M. Ocul Immunol Inflamm; Members of Scientific Committee of First International Workshop on Ocular Sarcoidosis International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS); 2009. p. 160-169.
24. Rahi AH, Addison DJ. Autoimmunity and the outer retina. Trans Ophthalmol Soc U K. 1983; 103(pt 4):428–437. [PubMed: 6611615]
25. Forooghian F, Adamus G, Sproule M, et al. Enolase autoantibodies and retinal function in multiple sclerosis patients. Graefes Arch Clin Exp Ophthalmol. 2007; 245:1077–1084. [PubMed: 17219105]
26. Lee JH, Cho SB, Bang D, et al. Human anti-alpha-enolase antibody in sera from patients with Behcet's disease and rheumatologic disorders. Clin Exp Rheumatol. 2009; 27(suppl 53):S63–S66. [PubMed: 19796536]
27. Vermeulen N, Arijs I, Joossens S, et al. Anti-alpha-enolase antibodies in patients with inflammatory bowel disease. Clin Chem. 2008; 54:534–541. [PubMed: 18218721]
28. Patel N, Ohbayashi M, Nugent AK, et al. Circulating anti-retinal antibodies as immune markers in age-related macular degeneration. Immunology. 2005; 115:422–430. [PubMed: 15946260]
29. Chan JW. Paraneoplastic retinopathies and optic neuropathies. Surv Ophthalmol. 2003; 48:12–38. [PubMed: 12559325]
30. Hooks JJ, Tso MO, Detrick B. Retinopathies associated with antiretinal antibodies. Clin Diagn Lab Immunol. 2001; 8:853–858. [PubMed: 11527791]

31. Ko AC, Brinton JP, Mahajan VB, et al. Seroreactivity against aqueous-soluble and detergent-soluble retinal proteins in posterior uveitis. Arch Ophthalmol. 2011; 129:415–420. [PubMed: 21482867]
32. Shimazaki K, Jirawuthiworavong GV, Heckenlively JR, et al. Frequency of anti-retinal antibodies in normal human serum. J Neuroophthalmol. 2008; 28:5–11. [PubMed: 18347451]
33. Jampol LM, Fishman GA. Immunosuppression for autoimmune retinopathy. Arch Ophthalmol. 2009; 127:573–575. [PubMed: 19365043]
34. Ohguro H, Ogawa K, Maeda T, et al. Cancer-associated retinopathy induced by both anti-recoverin and anti-hsc70 antibodies in vivo. Invest Ophthalmol Vis Sci. 1999; 40:3160–3167. [PubMed: 10586938]
35. Maeda T, Maeda A, Maruyama I, et al. Mechanisms of photoreceptor cell death in cancer-associated retinopathy. Invest Ophthalmol Vis Sci. 2001; 42:705–712. [PubMed: 11222531]
36. Chen W, Elias RV, Cao W, et al. Anti-recoverin antibodies cause the apoptotic death of mammalian photoreceptor cells in vitro. J Neurosci Res. 1999; 57:706–718. [PubMed: 10462694]
37. Adamus G, Machnicki M, Seigel GM. Apoptotic retinal cell death induced by antirecoverin autoantibodies of cancer-associated retinopathy. Invest Ophthalmol Vis Sci. 1997; 38:283–291. [PubMed: 9040460]
38. Shiraga S, Adamus G. Mechanism of CAR syndrome: anti-recoverin antibodies are the inducers of retinal cell apoptotic death via the caspase 9- and caspase 3-dependent pathway. J Neuroimmunol. 2002; 132:72–82. [PubMed: 12417436]
39. Adamus G, Webb S, Shiraga S, et al. Anti-recoverin antibodies induce an increase in intracellular calcium, leading to apoptosis in retinal cells. J Autoimmun. 2006; 26:146–153. [PubMed: 16426815]
40. Magrys A, Anekonda T, Ren G, et al. The role of anti-alpha-enolase autoantibodies in pathogenicity of autoimmune-mediated retinopathy. J Clin Immunol. 2007; 27:181–192. [PubMed: 17235687]
41. Ren G, Adamus G. Cellular targets of anti-alpha-enolase autoantibodies of patients with autoimmune retinopathy. J Autoimmun. 2004; 23:161–167. [PubMed: 15324934]
42. Adamus G, Amundson D, Seigel GM, et al. Anti-enolase-alpha autoantibodies in cancer-associated retinopathy: epitope mapping and cytotoxicity on retinal cells. J Autoimmun. 1998; 11:671–677. [PubMed: 9878089]
43. Ogra S, Sharp D, Danesh-Meyer H. Autoimmune retinopathy associated with carcinoid tumour of the small bowel. J Clin Neurosci. 2014; 21:358–360. [PubMed: 24126040]
44. Heckenlively JR, Aptsiauri N, Nusinowitz S, et al. Investigations of antiretinal antibodies in pigmentary retinopathy and other retinal degenerations. Trans Am Ophthalmol Soc. 1996; 94:179–200. discussion 200–176. [PubMed: 8981696]
45. Kikuchi T, Arai J, Shibuki H, et al. Tubby-like protein 1 as an autoantigen in cancer-associated retinopathy. J Neuroimmunol. 2000; 103:26–33. [PubMed: 10674986]
46. Adamus G, Karren L. Autoimmunity against carbonic anhydrase II affects retinal cell functions in autoimmune retinopathy. J Autoimmun. 2009; 32:133–139. [PubMed: 19269136]
47. Adamus G, Brown L, Schiffman J, et al. Diversity in autoimmunity against retinal, neuronal, and axonal antigens in acquired neuro-retinopathy. J Ophthalmic Inflamm Infect. 2011; 1:111–121. [PubMed: 21744285]
48. Lu Y, Jia L, He S, et al. Melanoma-associated retinopathy: a paraneoplastic autoimmune complication. Arch Ophthalmol. 2009; 127:1572–1580. [PubMed: 20008709]
49. Adamus G, Choi D, Raghunath A, et al. Significance of anti-retinal autoantibodies in cancer-associated retinopathy with gynecological cancers. J Clin Exp Ophthalmol. 2013; 4:307. [PubMed: 24672741]
50. Adamus G, Aptsiauri N, Guy J, et al. The occurrence of serum autoantibodies against enolase in cancer-associated retinopathy. Clin Immunol Immunopathol. 1996; 78:120–129. [PubMed: 8625554]
51. Terrier B, Degand N, Guilpain P, et al. Alpha-enolase: a target of antibodies in infectious and autoimmune diseases. Autoimmun Rev. 2007; 6:176–182. [PubMed: 17289554]

52. Pratesi F, Moscato S, Sabbatini A, et al. Autoantibodies specific for alpha-enolase in systemic autoimmune disorders. J Rheumatol. 2000; 27:109–115. [PubMed: 10648026]
53. Mosca M, Chimenti D, Pratesi F, et al. Prevalence and clinico-serological correlations of anti-alpha-enolase, anti-C1q, and anti-dsDNA antibodies in patients with systemic lupus erythematosus. J Rheumatol. 2006; 33:695–697. [PubMed: 16583471]
54. Adamus G, Bonnah R, Brown L, et al. Detection of autoantibodies against heat shock proteins and collapsin response mediator proteins in autoimmune retinopathy. BMC Ophthalmol. 2013; 13:48. [PubMed: 24066722]
55. Ohguro H, Yokoi Y, Ohguro I, et al. Clinical and immunologic aspects of cancer-associated retinopathy. Am J Ophthalmol. 2004; 137:1117–1119. [PubMed: 15183799]
56. Ohguro H, Ogawa K, Nakagawa T. Recoverin and Hsc 70 are found as autoantigens in patients with cancer-associated retinopathy. Invest Ophthalmol Vis Sci. 1999; 40:82–89. [PubMed: 9888430]
57. Forooghian F, Macdonald IM, Heckenlively JR, et al. The need for standardization of antiretinal antibody detection and measurement. Am J Ophthalmol. 2008; 146:489–495. [PubMed: 18672221]
58. Heckenlively JR, Fawzi AA, Oversier J, et al. Autoimmune retinopathy: patients with antirecoverin immunoreactivity and panretinal degeneration. Arch Ophthalmol. 2000; 118:1525–1533. [PubMed: 11074809]
59. Adamus G, Wilson DJ. The need for standardization of antiretinal antibody detection and measurement. Am J Ophthalmol. 2009; 147:557. author reply 557–558. [PubMed: 19217957]
60. Faez S, Loewenstein J, Sobrin L. Concordance of antiretinal antibody testing results between laboratories in autoimmune retinopathy. JAMA Ophthalmol. 2013; 131:113–115. [PubMed: 23307224]
61. Artsob H. Western Blot as a confirmatory test for Lyme disease. Can J Infect Dis. 1993; 4:115–116. [PubMed: 22346434]
62. Whitcup SM, Vistica BP, Milam AH, et al. Recoverin-associated retinopathy: a clinically and immunologically distinctive disease. Am J Ophthalmol. 1998; 126:230–237. [PubMed: 9727517]
63. 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; 139:780–794. [PubMed: 15860281]
64. Sen HN, Chan CC, Caruso RC, et al. Waldenstrom's macroglobulinemia-associated retinopathy. Ophthalmology. 2004; 111:535–539. [PubMed: 15019332]
65. Mahdi N, Faia LJ, Goodwin J, et al. A case of autoimmune retinopathy associated with thyroid carcinoma. Ocul Immunol Inflamm. 2010; 18:322–323. [PubMed: 20662664]
66. Or C, Collins DR, Merkur AB, et al. Intravenous rituximab for the treatment of cancer-associated retinopathy. Can J Ophthalmol. 2013; 48:e35–e38. [PubMed: 23561621]