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Rituximab for autoimmune retinopathy: Results of a Phase I/II clinical trial

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Abstract:

PURPOSE: This prospective study evaluates whether rituximab is a safe and potentially effective treatment for nonparaneoplastic autoimmune retinopathy (npAIR).

MATERIALS AND METHODS: Five npAIR patients were enrolled in a Phase I/II, prospective, nonrandomized, open-label, single-center study. All patients received a cycle of 1000 mg intravenous rituximab at weeks 0 and 2, with a second cycle of rituximab 6 to 9 months later. Clinical evaluation was performed at baseline, 6 and 12 weeks after each rituximab cycle, and then every 3 months for a total duration of 18 months. The primary outcome for this study was treatment success based on visual field and full-field electroretinography at 6 months. The secondary outcomes included treatment success at months 12 and 18, drug-related adverse events, changes in visual symptoms, and changes in quality of life.

RESULTS: Two patients met criteria for treatment success: one based solely on electroretinography and the other based solely on visual field area, but treatment success was not sustained. Clinical response over the course of the 18-month study showed disease stabilization in three patients and treatment failure in two patients. There were no severe drug-related adverse events.

CONCLUSION: This is the first clinical trial prospectively evaluating the effect of rituximab in npAIR and, although rituximab was well tolerated, there was no clear-cut clinical improvement conferred by B cell depletion with rituximab.

Keywords:

Autoimmunity, electroretinography, retinal degeneration, rituximab, visual fields

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Introduction

Autoimmune retinopathy (AIR) is a rare retinal disorder presumably caused by anti-retinal antibodies, with a subset of these antibodies demonstrating pathogenicity in animal disease models.[1,2] Essential diagnostic criteria for AIR include (1) visual dysfunction and electroretinography abnormalities not explained by an alternative diagnosis, (2) lack of intraocular inflammation, and (3) positive serum anti-retinal antibodies.[3]

There is no proven treatment for nonparaneoplastic AIR (npAIR).[3,4] If anti-retinal antibodies in npAIR are pathogenic, attenuating the autoimmune response may ameliorate disease. Rituximab (Rituxan, Genentech, South San Francisco, CA, USA)[5] is a monoclonal immunoglobulin (Ig) G antibody that depletes B cells.[6] Several case studies and series suggest that rituximab may be beneficial for AIR,[7-11] but these types of studies tend to preferentially report positive outcomes. This study provides the first prospective evaluation of rituximab for npAIR.

Materials and Methods

The protocol for this Phase I/II, prospective, nonrandomized, open-label, single-center

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study was approved by the applicable Institutional Review Board (protocol ID 10-EI-0040), complied with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. All methods were carried out in accordance with these guidelines and regulations. The study is registered at clinicaltrials.gov (NCT01086631, first submitted on March 12, 2010). In accordance with the prespecified study design, five npAIR patients were recruited. All patients provided written informed consent at study enrollment. The study was conducted from March 2010 to April 2014. It is important to note that the initiation of this study predates some of the published literature on the use of rituximab in AIR.

Rituximab dosing for this study was based on the treatment schedule for rheumatoid arthritis.[5] All five patients received an intravenous infusion of 1000 mg rituximab at study enrollment and at 2 weeks (first cycle of rituximab). Methylprednisolone 100 mg was administered intravenously 30 min prior to each rituximab infusion. Patients meeting criteria for treatment success or disease stabilization, as defined below, at 6 months, were eligible for a second cycle of rituximab unless there was a medical contraindication. All patients met the criteria for treatment success or disease stabilization at 6 months and received a second cycle of rituximab. The patients returned for a safety visit 6 weeks after each cycle of rituximab and otherwise were seen in clinic every 3 months until study completion at 18 months.

All study visits involved an ophthalmic history, questionnaires to assess patient-reported outcomes, concomitant medication assessment, history and physical examination by internal medicine, a detailed ophthalmic examination including best-corrected visual acuity (BCVA) and manifest refraction using Early Treatment Diabetic Retinopathy Study (ETDRS) methods, color vision testing by Ishihara plates, intraocular pressure monitoring by Goldmann applanation tonometry, slit-lamp examination, dilated fundus examination, 30–2 Humphrey visual field (HVF) testing, Goldmann visual field (GVF) testing, full-field electroretinography (ffERG), fundus autofluorescence (FAF), macular spectral domain-optical coherence tomography (OCT), and fluorescein angiography. Laboratory testing at each study visit included serum pregnancy testing in female patients with childbearing potential, basic metabolic panel, complete blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum IgA, serum IgM, serum IgG, and serum IgG subclasses when available.

Inclusion and exclusion criteria

The study patients were ≥18 years of age and had Snellen BCVA better than or equal to 20/200 in at least one eye. All patients had a diagnosis of npAIR at enrollment based on the presence of deficits on HVF and/or GVF, subnormal amplitudes and/or increased implicit times on ffERG, serum anti-retinal antibodies present by Western blot or immunohistochemistry, no alternative diagnosis to explain visual dysfunction, and an unremarkable age-appropriate malignancy evaluation which included a detailed physical examination by primary care physician, head magnetic resonance imaging and chest/abdomen/pelvis computed tomography (or positron emission tomography scan), complete blood count, serum chemistry, thyroid function tests on all patients and mammogram, Pap smear, prostate-specific antigen testing, and colonoscopy as indicated by age or gender. The study exclusion criteria included use of more than two immunosuppressive agents, use of another biologic immunosuppressive agent within 3 months of study enrollment, a change in immunosuppressive medications within 2 months of study enrollment, intraocular or periocular steroid injection within 2 months of study enrollment, intraocular surgery within 2 months of study enrollment, active infection at study enrollment, history of syphilis or tuberculosis, history of human immunodeficiency virus (HIV) and hepatitis B or C, history of cancer other than nonmelanoma skin cancer or non-Hodgkin's lymphoma within the past 5 years, a personal or family history of genetic retinal degenerative disease, and any medical condition that would contraindicate rituximab administration. Testing performed at study enrollment to rule out active or latent infection included chest X-ray, purified protein derivative skin test or Quantiferon-TB Gold, rapid plasma reagin, syphilis IgG, HIV, hepatitis B panel, and hepatitis C antibody.

Outcome measures

The primary outcome of this study was the number of treatment successes at 6 months. Prespecified criteria for treatment success were (1) ≥25% improvement in ffERG response amplitudes, (2) ≥3 dB improvement on 30–2 HVF mean deviation (MD), or (3) ≥25% improvement in GVF by averaging the change in area of field of view with the I-1e, I-4e, and V-4e isopters. Those not meeting criteria for treatment success qualified for partial response/disease stabilization if electroretinogram (ERG) response amplitudes were between 75% and 125% of baseline, 30–2 HVF MD was within 3 dB of baseline, and visual field area on GVF was between 75% and 125% of baseline. Patients were classified as treatment failures if they did not meet criteria for treatment success or disease stabilization. In addition, a *post hoc* analysis was conducted with 40% change criteria for ffERG because some ERG stimuli may show 40% or more intertest amplitude variability in normal controls and those with retinal disease.[12-14]

Secondary outcomes for this study included the number of treatment successes at 9, 12, and 18 months; the number of patients with disease stabilization at 6, 9, 12, and 18 months; changes in BCVA; leakage on fluorescein angiography; macular edema on OCT; FAF findings; and patient-reported outcomes. Quality of life was assessed with the National Eye Institute Visual Functioning Questionnaire – 25 (NEI VFQ-25).[15] Safety outcomes were the number and severity of adverse events, especially those likely to be related to the study drug, and the proportion of patients with loss of ≥15 ETDRS letters compared to baseline.

Results

Table 1 shows demographic information for the five npAIR study participants. The mean age was 53.8 years (median, 52 years), the majority of patients (80%) were female, and all were Caucasian. All patients showed only mild variability in visual acuity during the study, and no patient had loss of ≥15 ETDRS letters compared to baseline at any time point.

The systemic inflammatory diseases for patients 1, 2, and 5 [Table 1] were asymptomatic at study entry and patients 3 and 4 did not have systemic inflammatory disease, so rituximab treatment did not provide systemic symptomatic benefit. However, abnormal serum inflammatory markers at study entry in two of three patients did normalize after rituximab treatment. Patient 1 had elevated ESR (59 mm/h), which normalized to 25 mm/h at 6 weeks, and elevated serum IgG (2910 mg/dl, normal 642–1730 mg/dl), which decreased to 1780 mg/dl at 6 weeks and normalized to 1460 mg/dl at 6 months. Patient 3 had mildly elevated CRP (3.72 mg/L, normal <3.0 mg/L) and total IgG (1910 mg/dl), both of which remained mildly elevated throughout the study despite rituximab treatment. Patient 4 had mildly elevated CRP (4.88 mg/L), which normalized to 1.97 mg/L 6 weeks after the initial rituximab treatment and remained in the normal range until the 18-month study visit when CRP again was mildly elevated at 4.0 mg/L. ESR, CRP, IgG, IgM, and IgA otherwise were normal in the study patients.

ffERG amplitudes showed a high degree of variability [Figure 1]. There was a progressive decrease in light-adapted amplitudes in both eyes in patient 3, and in other patients, there was no consistent clinically important trend toward improvement or worsening of ERG amplitudes. ffERG implicit times remained stable over the course of the study for all patients. HVF MD values decreased by >3 dB compared to baseline in patient 2 starting at 6 months and in patient 3 at 18 months, while MD values in the other patients were stable [Figure 2]. Similarly, GVF analysis showed progressive visual field worsening in patients 2 and 3 [Figure 3]. Patients 4 and 5 did show a >25% increase in GVF areas for the inner isopters only; however, these patients did not have corresponding improvements in HVF MD values, and only patient 4 met GVF criteria for treatment success based on averaging all three study isopters. Patient-reported outcomes, measured by NEI VFQ-25 quality of life scores, remained relatively constant during the study [Figure 4].

Although this study was not specifically designed to test whether rituximab alters the rate of change of disease course, ffERG and GVF testing had been performed 3 months prior to the study enrollment in patients 1, 3, and 5, which allows a partial analysis of rate of change. Because the ffERG amplitudes and implicit times in all three of these patients showed stability at the first study visit compared to prestudy testing, the available prestudy testing does not alter interpretation of the ffERG study results. On the other hand, *post hoc* rate of change analysis suggests that rituximab may have prevented further visual field decline in one of the study patients: the GVF area for patient 1 declined between the prestudy visit and the initial study visit, then stabilized

Table 1: Study patient demographics, anti-retinal antibody testing, and prior and concomitant immunomodulatory therapy

Patient	Age (years)	Sex	Systemic disease	Anti-retinal antibody testing	Prior IMT	Concomitant IMT
1	65	Female	Sjogren's syndrome	IHC positive WB: 20 kDa, 48 kDa	Hydroxychloroquine	Cyclosporine (weeks 42-55)
2	41	Female	Sjogren's syndrome	IHC positive	Cyclosporine	Cyclosporine (weeks 0-78)
3	48	Female	None	IHC positive WB: 31 kDa, 32 kDa, 35 kDa	Prednisone, Cyclosporine, Mycophenolate mofetil	Mycophenolate mofetil (weeks 0-78), Methotrexate (weeks 69-78)
4	52	Male	None	IHC positive WB: 23 kDa (not recoverin), 41 kDa, 44 kDa, 45 kDa	None	None
5	63	Female	Inflammatory bowel disease*	IHC positive WB: Enolase (46 kDa)	Methotrexate	Methotrexate (weeks 0-78)

*Diagnosis was questionable; patient did not require treatment. IHC=Immunohistochemistry, IMT=Immunomodulatory therapy, WB=Western blot

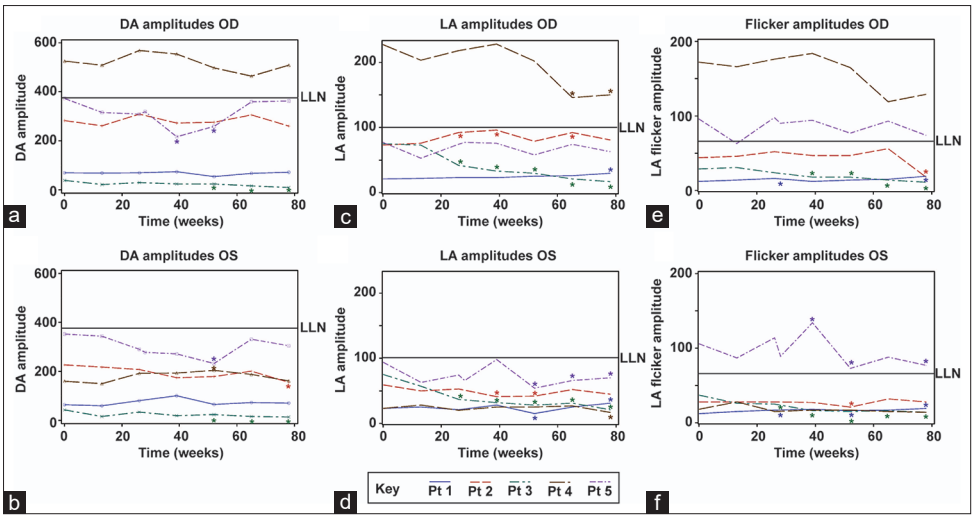

Figure 1: Full-field electroretinogram amplitudes. Dark-adapted b-wave amplitudes with 3 cd-s/m^2 stimulus in patients' right eyes (a) and left eyes (b), light-adapted amplitudes with 3 cd-s/m^2 stimulus in patients' right eyes (c) and left eyes (d), and light-adapted 30 Hz flicker amplitudes in patients' right eyes (e) and left eyes (f). Solid black lines denote lower limit of normal. *Indicates ≥ 25% change from baseline. DA = dark-adapted, LA = light-adapted, OD = right eye, OS = left eye

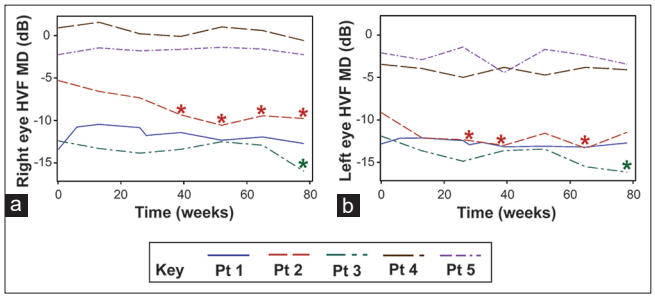

Figure 2: Humphrey visual field mean deviation of the study participants over time in patients' right eyes (a) and left eyes (b). *Indicates ≥3 dB change from baseline. HVF = Humphrey visual field, MD = mean deviation

after rituximab treatment. The rates of change in GVF area were similar before and after rituximab treatment for patients 3 and 5.

Based on initial study criteria with 25% ERG amplitude variability (i.e., considering a change >25% as an improvement in ERG), patients 2 and 4 were considered treatment successes at 26 weeks (with treatment success in only one of the three parameters for both) and the other three patients showed disease stabilization [Figure 5a]. Of note, although the improvement in ERG amplitudes classified patient 2 as a treatment success at 26 weeks, patient 2 met treatment failure classification by HVF MD. Furthermore, these improvements in ERG amplitudes were not sustained at week 52, and patient 2 met criteria for treatment failure at 78 weeks. The ERG treatment success in patient 4 at 52 weeks was driven solely by a 27.5% increase in the dark-adapted b-wave amplitude left eye; other ERG parameters showed stability in this patient at 52 weeks. *Post hoc* analysis requiring ≥40% change in ERG amplitude for a clinical difference showed overall disease stabilization in three patients and disease progression in two patients [Figure 5b]. Although the ERG amplitudes for patient 1 met criteria for treatment success at 78 weeks, this patient's ERG amplitudes were severely reduced throughout the study; therefore, in this case, a small change in amplitude produced a relatively large percentage change to meet the study criteria for treatment success despite maintaining severely reduced ERG amplitudes. Of note, two of the three patients that showed disease stability at 78 weeks were those with disease duration of <1 year at the time of study enrollment.

There were no serious study drug-related adverse events during the study. Infusion reactions occurred in three patients, but all were mild and resolved without sequelae. All infections were mild in severity and treated with antibiotics without long-term sequelae. One patient was diagnosed with papillary thyroid carcinoma at week 25, which was treated with thyroidectomy (without subsequent recurrence), so the second series of rituximab was delayed until 9 months to allow for cancer treatment.

Discussion

As the pathogenesis of npAIR is presumed to be antibody mediated, we hypothesized that impairing the B cell response would ameliorate disease. This is the first study to test this hypothesis in a prospective clinical study. There was no clear-cut clinical improvement with rituximab treatment in these npAIR patients based on multiple functional outcomes, with visual field and ffERG testing obtained at standardized time points up to 18 months. Three patients had disease stabilization with rituximab treatment, and two patients had disease progression. Interestingly, two of the three patients that showed disease stability at 18 months were those whose disease duration was <1 year at enrollment.

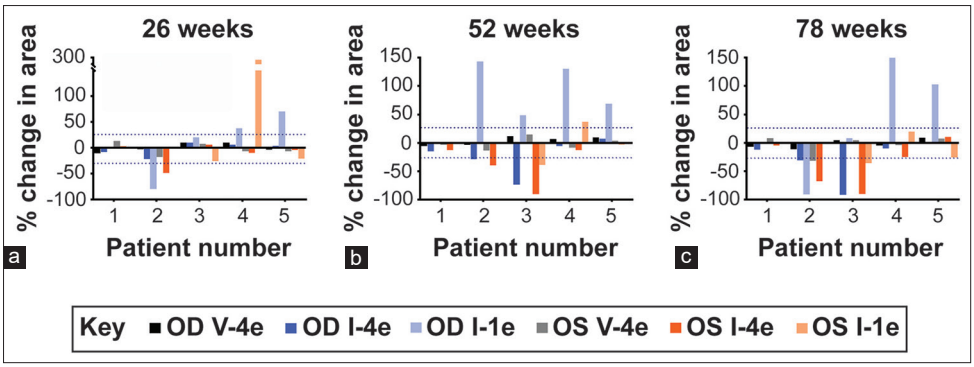

Figure 3: Percentage changes in Goldmann visual field isopter areas from baseline at 26 weeks (a), 52 weeks (b), and 78 weeks (c). Dotted lines indicate ≥25% change from baseline

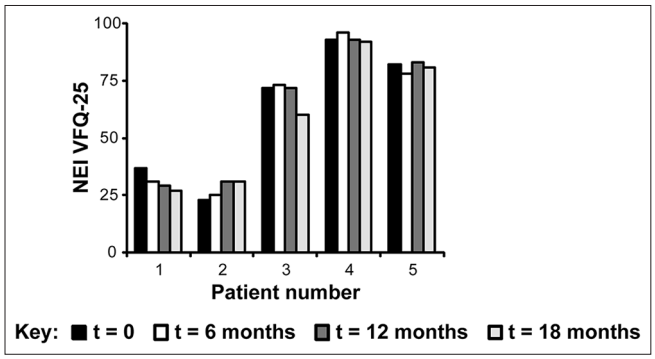

Figure 4: Changes in National Eye Institute Visual Functioning Questionnaire-25 scores at 0, 6, 12, and 18 months

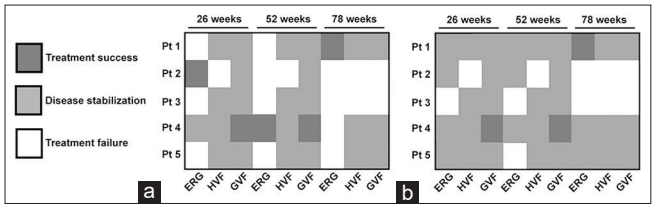

Figure 5: Treatment responses at 26, 52, and 78 weeks based on the study criteria with ≥25% (a) and ≥40% (b) difference in ERG amplitude for clinically meaningful change. ERG = electroretinogram, GVF = Goldmann visual field, HVF = Humphrey visual field

Analysis of patient-reported outcomes indicated that rituximab treatment was not associated with substantial symptomatic change in this study.

Our findings are consistent with those from a case series showing a mixed response to rituximab in npAIR patients, in which disease progression stabilized or worsened,[16] and a case showing no clinical improvement in a patient with Waldenström's macroglobulinemia-associated AIR 4 months after rituximab treatment.[17] However, other published reports of rituximab for AIR are more favorable. Three case reports suggest that rituximab may be an effective treatment for AIR, with improved visual acuity and visual field in a case of cancer-associated retinopathy,[7] improved visual acuity and outer retinal reconstitution on OCT 4 months after rituximab therapy in a case of cancer-associated retinopathy,[8] and improved visual acuity and ffERG amplitudes 1 month after rituximab therapy in a case of npAIR.[9] A retrospective case series indicates that some patients classified as npAIR show clinical improvement with rituximab,[10] though it is important to note that the majority of these patients had previously been diagnosed with other types of uveitis, namely lupus, birdshot chorioretinopathy, and HLA-B27-positive panuveitis and vasculitis, and thus would not be categorized as AIR according to consensus npAIR criteria.[3] The largest case series of rituximab treatment in AIR is more consistent with stabilization of disease: after rituximab infusions, there was an overall reduction in the rate of visual decline and stability in ERG, macular OCT, and adaptive optics scanning laser ophthalmoscopy parameters in a mixed population of cancer-associated retinopathy, melanoma-associated retinopathy, and npAIR patients.[11]

It is important to note that the diagnosis and pathogenesis of npAIR remains controversial and the criteria for inclusion in this study predate efforts to standardize clinical diagnosis of AIR. A consensus group statement provides diagnostic criteria for npAIR,[3] but there is no evidence that the antibodies found in these study patients are truly pathogenic. While detection of anti-retinal antibodies is a major component of this ill-defined disease, similar anti-retinal antibodies have been detected in uveitis patients and healthy controls.[18] The exact role of these autoantibodies remains elusive; it is possible that the antibodies are an epiphenomenon, at least in some cases, rather than a cause of disease. Western blot analysis of anti-retinal antibodies in our patient population shows that each patient has distinct anti-retinal antibodies, which complicates the analysis of pathogenicity; however, studying patients with similar anti-retinal antibody profiles is difficult given the rarity of npAIR. Additionally, even if we assume that the anti-retinal antibodies in npAIR are pathogenic, detection of these antibodies is not standardized; there is subjectivity in interpretation and discordance depending

on detection approach.[19,20] The common pattern that unifies this group of patients, in our experience, is the presence of abnormal ERG findings, anti-retinal antibodies, and disease progression in the absence of true intraocular inflammation and chorioretinal lesions. Histopathologic studies corroborate the lack of significant local inflammation while showing loss of photoreceptors and atrophic retina,[21] which may explain the lack of therapeutic response with immune modulatory agents in general.

Several limitations of this study are secondary to the rarity of npAIR, including a small sample size, lack of control population, and a heterogeneous population with disease at different stages and with different anti-retinal antibodies whose pathogenicity is unclear. In particular, given the absence of a control population, it is difficult to know whether disease stabilization was mediated by rituximab or merely represents the natural history of the disease. We excluded patients with a history of malignancy from enrolling in this study for a more homogeneous patient population, although we cannot rule out carcinoma-associated retinopathy in one study participant who developed papillary thyroid carcinoma during the study (and more than 5 years after her diagnosis of AIR).

There is no treatment for npAIR that has been proven effective. The approach to treating npAIR is extrapolated from paraneoplastic AIR; in that disease, the pathogenicity of anti-retinal antibodies and thus justification for immunomodulatory treatment is better established.[22] A consensus panel of uveitis experts recommends a trial of corticosteroids and then conventional immunosuppressant medications for npAIR,[3] with the acknowledgment that more evidence is needed to justify long-term immunomodulatory therapy. Our study does not show a clear therapeutic benefit for rituximab in npAIR; however, npAIR did not appear to progress in some of the study patients, and this study is underpowered to attribute this to the therapeutic effect, and the role of natural history cannot be ruled out.

Our study participants were fortunate to not experience significant drug-related side effects, but this likely is related to the small sample size as other studies show considerable risks of treatment with rituximab.[5] An important consideration with rituximab therapy is the potential for serious side effects, including severe infections, fatal infusion reactions, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy.

Conclusion

The lack of unambiguous improvement in this clinical trial indicates that rituximab does not provide definitive treatment for npAIR. Whether rituximab stabilizes disease in at least some cases of npAIR remains an open question. The need for treatment and the choice of treatment in npAIR should continue to be determined on a case-by-case basis until we have a better understanding of the pathogenicity of anti-retinal antibodies, natural course of AIR, and disease features.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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