Assessment of Th1, Th2, and Th17 Cells in Birdshot Retinochoroidopathy

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Introduction

Birdshot retinochoroidopathy (BSRC) is a chronic inflammatory disease that appears to be isolated to the eyes, causing distinct bilateral chorioretinal lesions, and progressive vision loss which can be treated with systemic immunomodulatory therapy (IMT). The pathogenesis has not been elucidated, but lymphocytic infiltration has been found on BSRC histopathology[1], and the role of retinal autoreactivity has been suggested[2]. T helper (TH)-17 cells, a subset of CD4+ T lymphocytes that produce interleukin (IL)-17 and are known to play an important role in uveitis and autoimmune disease, have recently been implicated in BSRC[3]. Kuiper et al. showed that IL-1β, IL-6, IL-17, and tumor necrosis factor (TNF)-α were elevated in the aqueous fluid of BSRC eyes. Furthermore, IL-1β, IL-17, and TNFα were more concentrated in the aqueous than in the serum. In another study, Monnet et al.[4] showed that interferon (IFN)-γ was elevated in the serum, but IL-17 and IL-23 were not. In this study, we will correlate the serum levels of 20 cytokines from the Th1, Th2, and Th17 pathways with disease activity and IMT in BSRC patients.

Methods

Single center cohort study of 15 BSRC patients, and 12 controls. The diagnosis of BSRC was based on the research criteria of an international consensus conference[5], and HLA-A29 positivity. Disease activity and IMT status, specifically CellCept and cyclosporin A, were recorded for each BSRC patient, and placed into the following subgroups: active disease naïve to IMT (n=3), active disease on IMT (n=3), remission on IMT (n=6), and remission off IMT (n=3). Disease activity was a clinical decision based on visual acuity, visual field, fundus exam, optical coherence tomography, fluorescein angiography, and electroretinography. Patients with other autoimmune disease, uncontrolled systemic disease, and recent surgery or infection within 1 month were excluded. Sera were collected and frozen until analysis. Heterophilic immunoglobulins were removed with protein L-coated agarose beads. Quantitative multiplex sandwich ELISA-based microarray assays were used to quantify 20 cytokines: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-17, IL-17F, IL-21, IL-22, IL-23, IL-28, IFNγ, macrophage inflammatory protein (MIP)-3α, transforming growth factor (TGF)-β1, TNFα, TNFβ, and granulocyte macrophage colony-stimulating factor (GM-CSF). Cytokine levels from BSRC patients were compared with controls and correlated with IMT and disease activity. Two-tailed T tests with a P value of 0.05 for significance was used.

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No financial disclosures for all authors

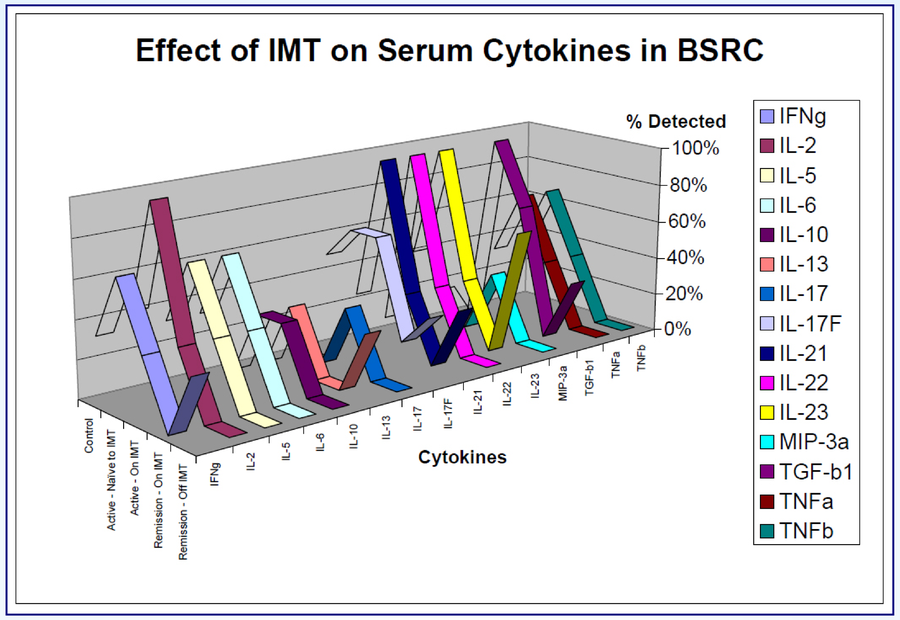

Figure 1: Percent of patients with serum cytokine levels above minimum levels of detection for controls (transparent ribbon) and BSRC subgroups (colored ribbon). Strong detection and downward trend with IMT is seen for IL-2, IL-21, IL-22, IL-23, and TGF-β1, but not IL-17. Note that IL-1β, IL-4, IL-12p70, and IL-28A were undetectable among all groups, and not displayed.

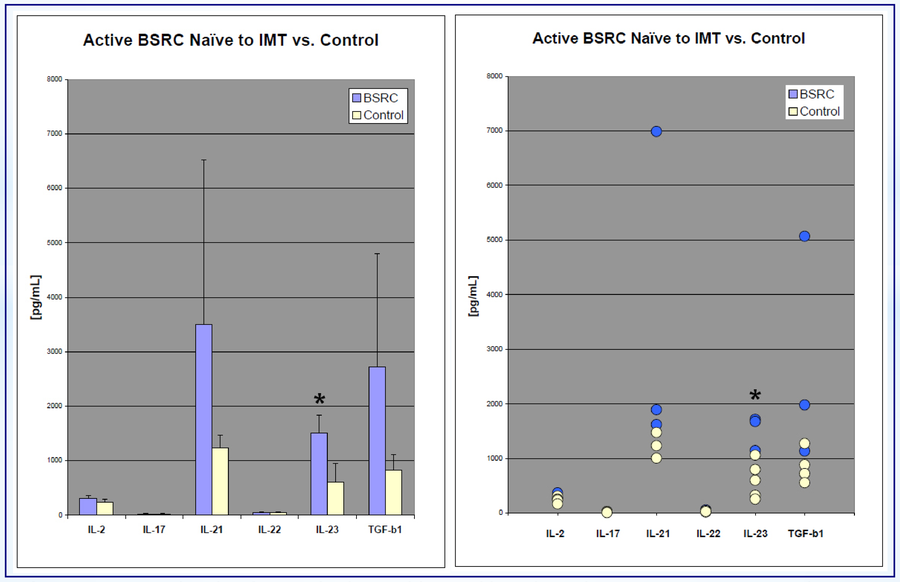

Figure 2: Serum levels of strongly detectable cytokines in active BSRC naïve to IMT (IL-2, IL-21, IL-22, IL-23, TGF-β1), and IL-17 are compared with controls. IL-23 levels are significantly elevated in active BSRC compared with controls. High variability limits statistical significance of IL-21 and IL-23, but the scatter plot shows a trend towards elevated levels.

Results

Serum IL-2, IL-21, IL-22, IL-23, and TGF-β1 were detectable in all active BSRC patients naïve to IMT as compared to a fraction of controls (figure 1). The percentage of detectable levels trended down with the use of IMT to nearly 0% for all cytokines in the remission on IMT subgroup. The serum level of IL-23 was significantly elevated in active BSRC patients naïve to IMT compared with controls (figure 2, asterisk; p=0.015). The significance of IL-21 and TGF-β1 levels was limited by n size and variability, but the scatter plot (figure 2 right panel) reveals a potential trend towards elevated levels. The serum levels of IL-2, IL-17, IL-22, as well as TNFα and INFγ (not shown) were not significantly different from control levels.

Discussion

While Kuiper et al. showed that IL-17 levels were elevated in the aqueous fluid of BSRC eyes, Monnet et al. showed that IL-17 was not elevated in BSRC serum, which is confirmed by our results. However, contrary to Monnet et al., we found no elevation in INFγ levels, and instead found IL-23 significantly elevated in active BSRC naïve to IMT. The differences in findings may be due to our subgrouping of BSRC patients, removal of heterophilic immunoglobulins, and use of microarray assays. In addition, n size is small, but the study is still undergoing additional recruitment. IL-23 is involved in chronic inflammation and the pathogenesis of autoimmune disease, probably via its maintenance and development of pathogenicity of Th17 cells, and promotion IL-17 and IL-6 production. Our finding suggests that elevations in peripheral levels of IL-23 in BSRC patients may play a role in promoting locally elevated levels of IL-17 and pro-inflammatory cytokines in the eye. If this is true, systemic therapy targeted against IL-23 may prove to be useful in the management of BSRC.

Conclusion

Serum levels of IL-23 are significantly elevated in active BSRC patients naïve to IMT. Taken together with other studies, these results suggest that the IL-23/IL-17 pathway may play an important role in the pathophysiology of BSRC.

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Efficacy of Combined Cyclosporine A and Mycophenolate Mofetil in the Treatment of Patients with Birdshot Retinochoroidopathy

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Introduction

BSRC is a bilateral, chronic idiopathic posterior uveitis characterized by vitritis and multiple hypopigmented lesions (Figure 1). Patients usually complain of progressive, debilitating vision loss even in the face of 20/20 Snellen visual acuity, which reflects the progression of retinal damage; moreover, this may occur in the absence of evident clinical findings (i.e. frank vitritis or vasculitis). Untreated patients eventually progress to functional blindness.

Serial ERG and fluorescein angiograms are of utmost help to assess the progression of deterioration of retinal function and to support clinical decision making in treating patients with BSRC.

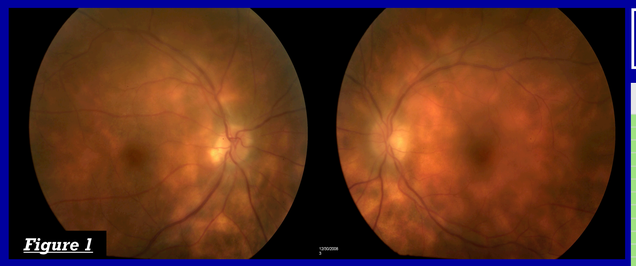


Figure 1

Several IMT regimens have been explored in efforts aimed at induction of a durable remission without the risks of long-term corticosteroid therapy. However, there is no published consensus providing a guideline for BSRC treatment.

We have reported the efficacy of CsA monotherapy at induction of remission; however, this required years of treatment rather than durable remission or cure after 2 years of therapy. We herein report the results of the use of combination of CsA and Mycophenolate mofetil in 40 patients with BSRC during a period of 12-months.

Methods

- Retrospective, non-comparative, interventional case series.
- Eighty eyes of 40 patients with BSRC who received CsA and MM for a minimum of one year.
- All patients were followed for at least five visits during the study.
- Outcome measures included BCVA logMAR, vitreous inflammation, FA features, ERG recordings, reported side effects to therapy, and number of relapses.
- Student's t-test, Pearson's chi-square test, and Fisher's exact test were used for statistical analysis

Results

		AGE at disease presentation (years)	HLA A29	Uveitis F/U time (months)	Systemic Associations	Corticosteroid before IMT	Previous IMT
1	M	43	Positive	129	HTN, Psoriasis	None	None
2	F	36	Positive	83	HTN	None	None
3	M	49	Positive	56	None	PRD PO	None
4	F	51	Positive	84	HTN	None	None
5	F	57	Positive	50	Breast cancer, Kidney tumor	None	None
6	F	42	Positive	96	None	None	None
7	F	46	Positive	95	EBV infection	PRD PO	None
8	F	53	Positive	72	Hashimoto's Thyroiditis, HC	PRD PO	CSA
9	M	62	Positive	77	HTN	None	None
10	F	67	Positive	63	HTN, HC	None	None
11	F	31	Positive	131	None	None	None
12	M	50	Positive	78	None	None	None
13	F	39	Positive	35	HypoT3	PRD PO	None
14	F	27	Positive	287	HypoT3	None	None
15	M	66	Positive	151	HTN, HC	None	CSA
16	M	49	Positive	155	HTN, HC, CAD	None	None
17	M	34	Positive	124	HC	None	None
18	F	45	Positive	68	Thyroid nodule	TSK	None
19	M	46	Positive	56	HC	PRD PO	None
20	M	52	Positive	24	None	None	None
21	M	62	N/A	83	DM2, carotid disease	TSK	None
22	F	46	N/A	120	IBD	TSK, IVK	None
23	M	50	Positive	20	HC, pericarditis	None	None
24	M	54	N/A	13	None	None	None
25	F	76	N/A	129	HC, HTN	None	None
26	F	47	Positive	151	IBD	PRD PO, TSK	None
27	F	71	Positive	40	Hypot3, HTN, HC	None	None
28	F	54	Positive	31	Psoriasis, asthma, goiter	None	None
29	M	52	Positive	24	None	None	None
30	F	48	Positive	96	None	None	None
31	M	49	Positive	27	None	PRD PO	None
32	M	50	Positive	21	Osteoarthritis	PF1%	MTX
33	F	53	Positive	56	Eczema	None	None
34	M	40	Positive	731	Colon Cancer, HTN	PRD PO, TSK	None
35	M	45	N/A	288	COPD	PF1%, PRD PO	CSA
36	M	36	Positive	168	None	PF1%, PRD PO	None
37	F	59	Positive	27	DM2, HTN, HC	None	None
38	M	36	N/A	372	HTN	PRD PO, IVK	CSA
39	F	47	Positive	71	None	PRD PO	None
40	M	60	Positive	196	HTN, HC, CAD	PRD PO, PF1%	None

Abbreviation list: HLA: Human Leucocyte Antigen, F/U: Follow up, IMT: Immunomodulatory therapy, HTN: Hypertension, PRD PO: Oral Prednisone, HO: History of, EBV: Epstein Barr Virus, HC: High cholesterol, HypoT3: Hypothyroidism, CAD: Coronary artery disease, TSK: Transepital Kenalog®, N/A: Not available, IBD: Inflammatory bowel disease, IVK: Intravitreal Kenalog®, PF1%: Prednisolone acetate 1%, COPD: Chronic Obstructive Pulmonary Disease, DM2: Diabetes Mellitus type 2.

Patient number	*IMT Time (months)*	*Total F/U Time since IMT*	*CSA Dose (mg/day)*	*MM Dose (mg/day)*	*Treatment Outcome*
1	96.6	112.1	100	2	Success
2	46.7	72	300	3	Success
3	42.5	54.1	200	1	Success
4	41	49.3	200	2	Success
5	19.6	51.9	200	1	Success
6	39	84	250	3	Success
7	19.1	67.1	300	2.5	Success
8	16.8	53.6	100	2.5	Success
9	37.1	77	200	2	Success
10	40.3	74.1	100	2	Success
11	33.7	68.8	300	3	Failure
12	56.8	93.9	300	2	Success
13	16.8	54.2	300	3	Success
14	84.6	141.1	200	2	Success
15	79.3	153.5	200	2	Success
16	95.8	120	200	2.5	Success
17	62.2	108	200	2	Success
18	39.1	53.6	300	2	Success
19	20	58.6	200	2	Success
20	15.2	23.3	200	3	Success
21	23.1	30.7	200	2	Success
22	17.8	26.5	200	2.5	Success
23	12.6	19.7	200	2	Success
24	13.1	48.6	300	2	Success
25	48.7	63.5	100	1.5	Success
26	18.4	26.7	200	2	Success
27	30.4	40.7	200	3	Success
28	28.8	29.8	300	3	Success
29	17.4	24.3	300	2	Success
30	23.2	85	100	2	Success
31	14.1	21.8	300	3	Success
32	11	20.9	200	2	Failure
33	44.2	53.4	150	2	Success
34	18	26	200	2	Failure
35	11	22.8	100	2.5	Success
36	28	36.6	300	2	Success
37	16.5	28.8	200	2	Success
38	18.6	25.9	200	2	Success
39	30.7	37.6	200	3	Success
40	15.5	23.1	200	3	Success

Table 2. Mean logMAR BCVA were not statistically significantly different after 1-year in either eye (p=0.434; p=0.180). Thirty-seven patients (92.5 %) achieved inflammation control at the 1-year endpoint.

Side Effects

During 12-month period	Frequency	During entire follow-up	Frequency
None	20	None	14
HTN	7	High blood risk abnormalities	13
Fatigue	4	*Anemia*	*3*
High blood risk abnormalities	6	*BUN/Cr elevation*	*7*
Anemia	*2*	*Leukopenia*	*3*
BUN/Cr elevation	*3*	*Transaminases elevation*	*1*
Leukopenia	*1*	HTN	9
GI upset (i.e discomfort, nausea)	7	GI upset	5
Headache	3	Fatigue	4
Hypercholesterolemia	3	Headache	2
Alopecia	1	Hypercholesterolemia	2
Body aches	1	BUN elevation	1
Dry mouth	1	Diarrhea	1
Dyspnea	1	Nausea	1
Leg cramps	1	Shingles	1
Numbness	1	Sinus infection	1
Neuropathy	1		
Shingles	1		
Upper respiratory tract infection	1		

*BUN: blood urea nitrogen; Cr: creatinine; GI: gastrointestinal; HTN: hypertension

Table 3. Only one patient failed to complete the 12-month period of therapy due to severe fatigue. Other side effects were transient and resolved after lowering or withholding IMT for a few weeks in all patients.

We analyzed the results of combined therapy over a total follow up time of 52.6 months (19.7-60.0). 65% of patients did not relapse over the entire follow-up time. 27% of these patients achieved durable remission off IMT after at least 2 years of treatment (median f/u time off IMT was 36.67 months). Moreover, another 29.7% of patients continue to be in remission while on long term IMT. Nine patients had to be transitioned to biologic response modifiers to achieve control.

Figure 2. Comparisons of electroretinogram 30 Hz amplitude and 30 Hz implicit times revealed no significant reduction between baseline and 1-year values for either eye (p=0.14 OD; p=0.17 OS).

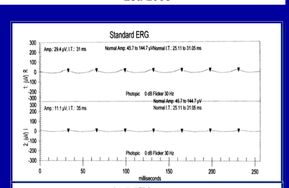
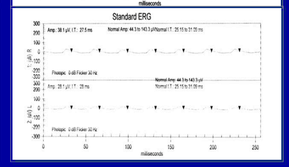
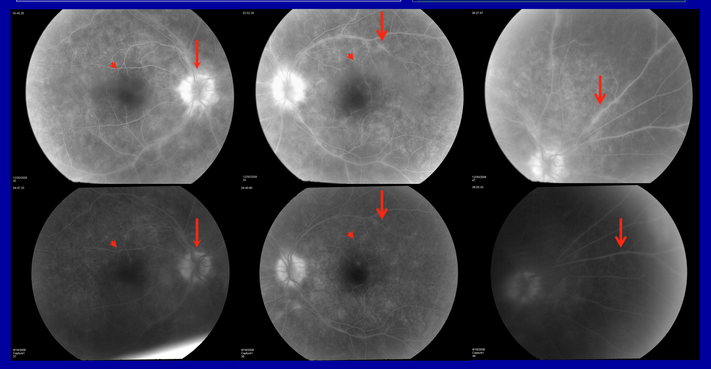


Figure 3. Vitreous inflammation scores, vasculitis and cystoid macular at baseline and at 1-year were highly statistically significantly reduced in both eyes (p<0.0001; p=0.025; p<0.001).





Conclusions

Several attempts to manage BSRC using CsA alone, MTX alone or other different IMTs have been reported. In the current series, adding MM to CSA resulted in inflammatory control and ERG parameters stabilization in 92.5% of patients in less than one year.

All of these patients were able to maintain remission off any kind of steroids after one year.

The long term results suggest that a 2-year period on combined therapy followed by a slow taper of IMT induces durable remission in a majority of patients (measured by FA/ERG). Moreover, this strategy has allowed 6 of our patients to be off IMT for a median of over 3 years.

Frequent follow up and high risk blood monitoring are mandatory for detecting occult side effects and reducing the likelihood of needing to discontinue therapy.

These data suggest that CsA/MM therapy is well-tolerated and efficacious in controlling inflammation and stabilizing vision for the majority of patients with BSRC.

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Infliximab Treatment of Patients with Birdshot Retinochoroidopathy

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Introduction

Birdshot retinochoroidopathy is a bilateral, progressive ocular inflammatory disease leading to painless visual loss. It is characterized by multiple, distinctive, ovoid, hypopigmented retinal pigment epithelial and choroidal lesions. Because of the chronicity of BSRC, systemic corticosteroid therapy is not effective for long term therapy, and causes its well-known inevitable side effects as well. Immunomodulatory therapy (IMT) can be tolerated for prolonged periods without life altering complications, and has been shown to preserve visual function in patients with BSRC. However, not every patient with BSRC is able to achieve durable corticosteroid-free remission with conventional IMT. In refractory cases infliximab may be an effective alternative treatment for these patients.

Methods

All refractory birdshot retinochoroidopathy patients from July 2005 to October 2011 were identified from retrospective chart review. All patients received 4-5 mg/kg of Infliximab at 4-8 week intervals. Demographic data, use of immunosuppressive drugs, biologic agents, and reason for conventional therapy discontinuation were gathered. Disease activity monitoring including signs of ocular inflammation, fluorescein angiography (FA) evidence of retinal vasculitis or papillitis, indocyanine green angiography (ICG) evidence of active choroiditis, electroretinography (ERG) parameters indicative of active or worsening of retinal functions, and optical coherence tomography (OCT) findings indicative of static or worsening macular edema were recorded. The outcome features of primary interest were abolition of all evidence of active inflammation, improved visual acuity (VA), and presence of cystoid macular edema (CME). Corticosteroid-sparing success was defined as inactive inflammation after tapering prednisone to ≤ 10 mg per day.). We assessed the outcomes of infliximab therapy at 6 months and 1 year follow up. Adverse events of Infliximab were also tabulated.

Results

Mean duration of disease before starting infliximab was 58.62 months. Mean duration on Infliximab was 13.55 months. Prior to Infliximab therapy, all patients received and failed conventional immunosuppressive therapy. Ten patients had received another biologic agent.

Table 1 shows clinical characteristics of the study population

Patient-specific characteristics	
Number of patients	22
Median age (range)	53 (29-74)
Gender (%female)	77.27
Race (% white)	100
HLA A29 (%positive)	95.45
Bilateral involvement (%)	100
Prior Mycophenolate mofetil (%)	95.45
Prior Cyclosporin (%)	90.91
Prior Sirolimus (%)	13.64
Prior Methotrexate (%)	13.64
Prior Daclizumab (%)	45.45
Mean duration on Infliximab (month)	13.55
Mean duration of disease before starting infliximab (month)	58.62
Eye-specific characteristics	
Number of eyes	44
Active disease (%)	59.09
Inactive disease (%)	40.91
VA 20/40 or better before treatment (%)	84.09
CME (%)	22.73

Table 2 summarizes the outcomes

Patients	Number	Percent (95% CI)
At 6 months (n=18)		
Control of inflammation	9/11	81.82 (47.76-96.79)
Infliximab combined with other IMT	8/18	44.44 (22.40-68.65)
Corticosteroid-sparing success	18/18	100 (78.12-100)
At 1 year (n=9)		
Control of inflammation	3/4	75 (21.94-98.68)
Infliximab combined with other IMT	3/9	33.33 (9.04-69.08)
Corticosteroid-sparing success	9/9	100 (62.88-100)
Achieve remission after initiating therapy	19/22	86.36 (64.03-96.41)
Relapse (active inflammation during therapy)	3/22	13.64 (3.59-35.97)
Eyes	**Number**	**Percent (95% CI)**
At 6 months		
Active disease	3/36	8.33 (2.18-23.59)
Inactive disease	33/36	91.67 (76.41-97.82)
Remain inactive	12/12	100 (69.87-100)
CME	5/36	13.89 (5.23-30.29)
VA 20/40 or better	33/36	91.67 (76.41-97.82)
Control of inflammation	19/22	86.36 (64.03-96.41)
At 1 year		
Active disease	2/18	11.11 (1.95-36.7)
Inactive disease	16/18	88.89 (63.93-98.05)
Remain inactive	10/10	100 (65.55-100)
CME	1/18	5.56 (0.29-29.38)
VA 20/40 or better	17/18	94.44 (70.62-99.71)
Control of inflammation	6/8	75 (35.58-95.55)

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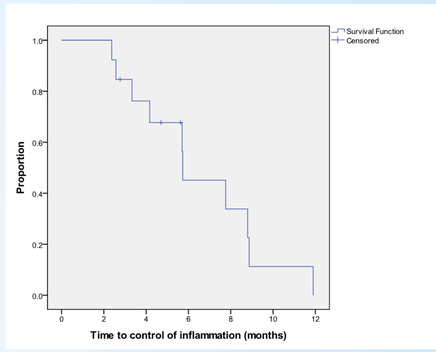
After initiating Infliximab, control of inflammation was achieved in 81.82% at 6 months and 75% at 1 year follow up. Three patients had active inflammation during therapy. Cystoid macular edema decreased from 22.73% at baseline to 13.89% at 6 months and 5.56% at 1 year after receiving the drug. Initial visual acuity 20/40 or better was found in 34 eyes (84.09%). At 6 months and 1 year, 91.67% and 94.44% of eyes respectively had VA 20/40 or better.



Graph 1 shows time to control of inflammation after initiating therapy

Six patients developed adverse events: infliximab therapy was not continued in these patients due to neuropathy, drug induced lupus, allergic reaction, and fungal infection.

Discussion

The effectiveness of infliximab in BSRC has been reported in few small case series so far. Suhler and colleagues found infliximab to be effective in refractory uveitis with 78% success rate at 10 weeks and 77% at 2 years. Baughmann et al. reported all 14 patients with various ocular inflammatory conditions had improvement of inflammation. Lindstedt and colleagues collected 13 cases of refractory uveitis and demonstrated that infliximab was effective in the treatment of ocular inflammation. Since all of these sources reported infliximab treatment in noninfectious uveitis and had few Birdshot cases in their series, the strength of this study is in being the first and largest report of infliximab treatment for BSRC.

Conclusion

The data suggest that Infliximab may be effective for controlling inflammation in otherwise treatment refractory cases of BSRC.

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2793.Risk factors associated with relapse of Birdshot Retinochoriodopathy

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Introduction

Birdshot retinochoroidopathy (BSRC) is a chronic, bilateral, posterior form of uveitis which is a relatively rare and occurs in 7.9% of patients with posterior uveitis. It tends to occur between 35 - 70 years of age, with the average age of presentation being 50 years. [1] Management of the patient with BSRC can be challenging as the disease has a chronic protracted course, which makes it difficult to assess progression, effect of treatment and need for further treatment.

Disease activity is monitored in one or more of the following ways: slit-lamp examination, fluorescein angiography (FA) fig 1, indocyanine green angiography (ICG) and electroretinigrams (ERG) fig 2. The purpose of this study was to evaluate the risk factors for relapse of BSRC patient after treatment with immunomodulatory therapy.

Methods

Chart review of 37 patients diagnosed with BSRC who were treated successfully with immunomodulatory therapy (IMT) and those who remained in remission for one year off all IMT was performed.

The following data were noted for each patient: age, gender, presence of HLA-A29 haplotype, type of IMT, visual acuity (VA), any associated systemic disease and family history of other autoimmune diseases. We subdivided the patients into two groups. Group "A "included patients who continued to be in remission off immunomodulatory therapy for more than 1 year. Group "B" were patients who had relapse of disease after a durable drug free remission of at least 1 year.

Comparison of the two groups was performed using independent t-test. Categorical data were analyzed using the chi-square test and P values, P< 0.05 was considered significant and P<0.001 was considered highly significant.

Results

There were 19 males (51.4%) and 18 female (48.6%). The mean age was 54 (SD 11.019) and 47.00 (SD 11.225) in Group-A and Group-B, respectively, with a range of 25 to 78 years.

There is a statistically significant difference in age at disease onset between the two groups; majority of the patients in Group A were above 50 years of age (n=17) compared to Group B (n=2), (P=0.02). Greater number of patients in Group A had symmetric eye involvement (n=22) as compared to Group B (n=4) (P=0.05). The two groups did not differ in terms of family history of autoimmune diseases and positive history of other autoimmune and systemic diseases.

Table. Analysis of risk factors in the Non recurrent and the recurrent group

	Group-A *N(27)*	Group-B *N(10)*	P value *(Chi square)*
Gender			
Male	12	7	0.167(1.908)
Female	15	3	
Age			
≥ 50	17	2	0.02*(5.392)
< 50	10	8	
HLA-A29			
positive test	16	9	0.137(2.211)
negative test	4	0	
Visual acuity affected			
Symmetrical	22	4	0.05*(7.776)
Asymmetrical			
Right eye	0	1	0.573
Left eye	5	5	0.260
Family H/O autoimmune disease	13	7	0.236(1.403)
Positive	14	3	
negative			
Patient H/O other autoimmune disease	9	5	0.353(0.892)
Positive	18	5	
negative			
Type of IMT used			0.081(16.719)
Cyclosporin	24	8	
Cellcept	25	5	
Methotrexate	3	0	
Others	1	1	
Non	0	1	
Duration of IMT *mean(SD)*	60.7 (49.28)	25.86 (14.06)	0.002*
Corticosteroids used			0.002*(15.310)
None	16	2	
Oral	2	6	
Parentral	2	2	
Intravitreal Inj. & Retisert	7	0	

In eighteen cases, immunosuppressive drugs were used alone (without corticosteroids), 16 of these cases were in Group A and only 2 were in Group B. This was statistically significant (P=0.002). The mean duration of IMT was significantly longer in Group A compared to Group B (60.7 ±49.28 vs. 25.86 ±14.06; P 0.002).

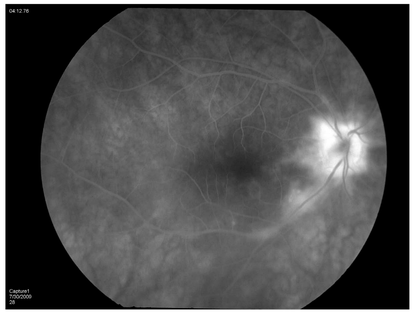

Fig. 1: Flourescin Angiography Shows active BSRC RT eye

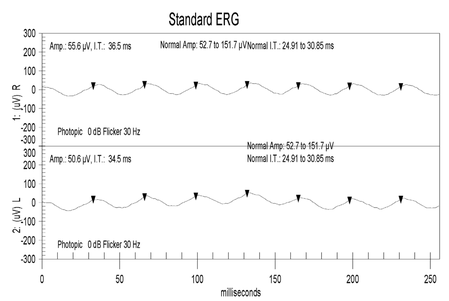

Fig. 2: ERG shows delayed IT and low Amplitude

Discussion

Our study demonstrates that patients who relapsed after successful treatment with immunomodulatory drugs and a durable remission of 1 year off IMT had early age of disease onset <50 years, asymmetric visual acuity at presentation, and received immunomodulatory treatment for lesser duration as compared to patients who continued to be in remission.

Patarroyo et al. have reported that there are certain autoimmune diseases where early onset of disease is associated with poor prognosis. [2] Similarly we found that patients with early onset disease < 50 years had comparatively greater chances of relapse. Rothova and associates have reported strong association between VA at disease onset and the visual outcome after 5-10 years in BSCR patients. Symmetric visual acuity at disease onset was found in 75.4% patients. [3] Patients with asymmetric visual acuity at presentation had greater chances of relapse.

Another interesting finding of our study was that (60%) patients in the relapse group received oral corticosteroids as compared to (7.4 %) in remission group (P=0.002). This finding is similar to the optic neuritis treatment trial (ONTT) which showed increased recurrence in patients of optic neuritis treated with oral corticosteroids. [4]

Conclusion

To conclude our study suggests that the patients with early age of onset of BSRC disease < 50 years, those treated with oral corticosteroids and shorter duration of IMT are more likely to relapse over time.

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Regulatory T-Cells In Peripheral Blood of Patients With Birdshot Retinochoroidopathy

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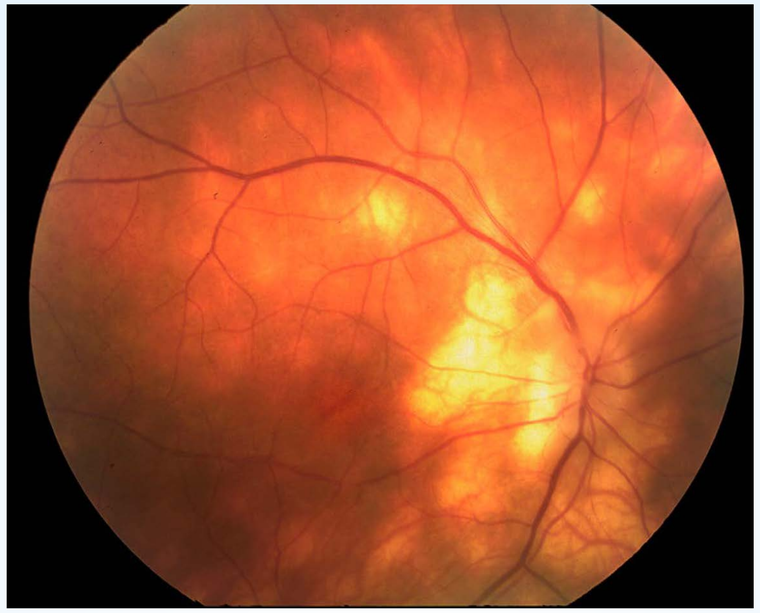
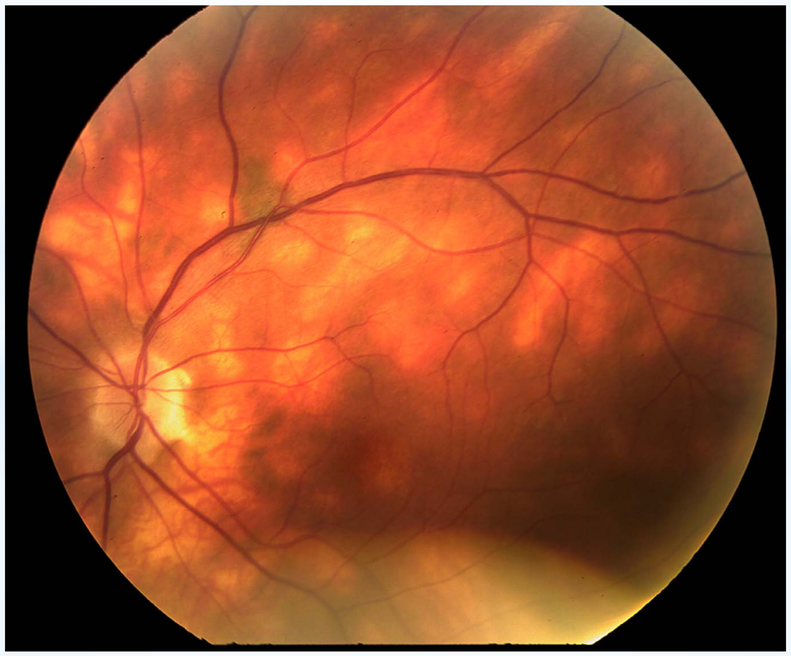
Introduction

Birdshot retinochoroidopathy (BSRC) is a chronic inflammatory disease which appears to be isolated to the eyes, causing distinct bilateral chorioretinal lesions, and progressive vision loss, treatable with systemic immunomodulatory therapy (IMT). The pathogenesis has not been elucidated, but lymphocytic infiltration has been found on BSRC histopathology[1], and the role of retinal autoreactivity has been suggested[2]. BSRC has been strongly linked to human leukocyte antigen A29 (HLA-A29). At present, the most probable hypothesis is that HLA-A29, by molecular mimicry, predisposes to autoimmunity against retinal and/or choroidal antigens, with an infectious or non-infectious agent acting as a trigger to the immune reaction. As yet, the trigger of presumed autoreactivity in BSRC is not known. Regulatory T cells (Tregs) are another important element described in the development of autoimmunity and CD4+ CD25+ FOXP3+ T cells represent this Treg comportment. We assessed the percentage of T regulatory cells in the peripheral blood of patients with active BSRC and compared this to normal persons.

Methods

This was a single center prospective study of 5 BSRC patients, and 5 controls, approved by the New England Institutional Review Board. Blood from patients between the ages of 30 and 70 years, with the diagnosis of birdshot retinochoroidopathy, naïve to IMT, and healthy individuals as controls was collected from April 2010 to December 2011. The diagnosis of BSRC was based on the research criteria of an international consensus conference[3], and HLA-A29 positivity. All the patients were enrolled from Dr. C. Stephen Foster's patient pool at the Massachusetts Eye Research & Surgery Institution. Flow cytometry was used for analysis of the percentage of CD4+ CD25+ FOXP3+ T regulatory cells in blood specimens. A sequential gating method was used to analyze FOXP3 data. First, a gate was placed around the population of events that are CD45+ and low in side scatter and were labeled as lymphocytes. Cells that fell within the lymphocyte gate and were CD3+CD4+ were labeled CD4+ T cells. CD25 expression on the CD4+ T cell population was gated as follows: CD25high+, CD25low+ and CD25-. FOXP3 expression on all three populations was analyzed and the percentage of FOXP3 positive versus negative was determined. Two-tailed T test with a P value of 0.05 for significance was used.





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No financial disclosures for all authors

Results

Blood CD4+ CD25+ FOXP3+ T regulatory cells were detectable in all active BSRC patients naïve to IMT as well as controls. The percentage of Tregs in BSRC patients was lower (86.2%) as compared to controls (100%). These results were statistically significant with a p value of less than 0.008.

Discussion

The role of CD4+ CD25+ FOXP3+ T regulatory cells has been established in the pathogenesis of systemic autoimmune disorders such as diabetes mellitus, rheumatoid arthritis and systemic lupus erythematosus. Ocularly, Tregs were implicated in diseases such as Behcet's[4] and Vokt-Koyanagi-Harada (VKH) syndrome[5]. Significantly lower percentages of CD4+ CD25+ FOXP3+ T regulatory cells were found in patients with active VKH and Behcet's disease. Similarly, we have demonstrated for the first time in a prospective study, the percentages of CD4+ CD25+ FOXP3+ T regulatory cells in patients with birdshot retinochoriodopathy and have established that the percentage is lower in BSRC patients. This may suggest that CD4+ CD25+ FOXP3+ T regulatory cell dysregulation might play a role in BSRC. Further studies are needed. The number of patients in our study was low.

Conclusion

Blood levels of CD4+ CD25+ FOXP3+ T regulatory cells are significantly lower in active BSRC patients naïve to IMT as compared to healthy individuals. Thus, we conclude that Treg deficiency may play an important role in the pathophysiology of BSRC.

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