

Alternate day vs daily topical brinzolamide in the treatment of cystic maculopathy in inherited rod cone retinal degenerations

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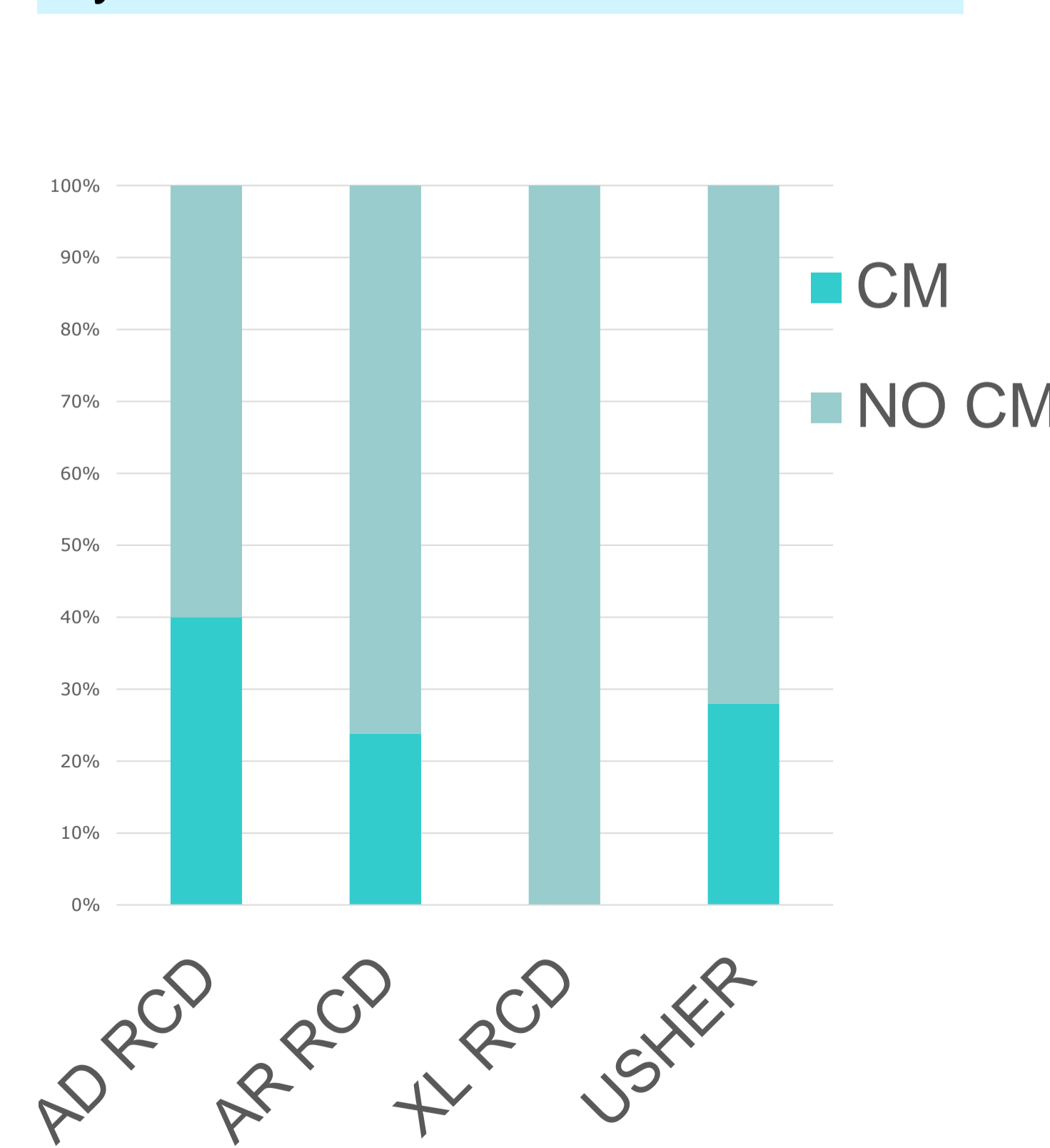
Purpose: Cystic maculopathy (CM) occurs in 10-50% of all inherited rod cone retinal degenerations (RCD), further compromising the small remaining central field of vision. Oral and topical carbonic anhydrase inhibitors, have been used with some effect, but rebound can occur. Discontinuation or Alternate day treatment with topical Brinzolamide may alleviate this effect. We assessed treatment response in alternate day vs continuous day dosing.

Methods: Retrospective chart review of patients with RCD from the New Zealand database of Inherited Retinal Disease. Outcomes were objective vision (VA) (≥7 letters significant), subjective VA, OCT analysis including reduction of cyst size, central macular thickness (CMT) (≥11% significant), and macular volume (MV). Treatment response was correlated with inheritance pattern and genotype. Multiple logistic regression was used to analyse the data.

Table 1. Baseline Characteristics of RCD and Usher Syndrome Patients in Study

	Total Patients n=255	Patients with CM n=62
Age, yrs (SD)	46.0 (15.4)	45.4 (18.7)
Female gender, n (%)	127 (49.8%)	34 (54.8%)
Rod Cone Dystrophy		
Autosomal dominant, n (%)	60 (23.5%)	24 (38.7%)
KLHL7	2	2
PRPF31	5	4
RHO	10	3
NRL	3	3
RP1	4	1
RDS (Peripherin2)	3	2
IMPDH1	2	0
Unknown	31	9
Autosomal recessive, n (%)	106 (41.6%)	26 (41.9%)
MERTK	1	1
PDE6B	8	2
USH2A	4	1
EYS	5	1
RP1	1	1
CNGA1	2	1
CRB1	3	0
Unknown	82	19
X linked, n (%)	38 (14.9%)	0 (0%)
Sporadic, n (%)	25 (9.8%)	6 (9.7%)
Usher Syndrome, n (%)	26 (10.2%)	6 (9.7%)
USH2A (USH2A)	14	3
MYO7A (USH1B)	8	1
CDH23 (USH1D)	1	1
Unknown	3	2

Figure 1. Distribution of cystic maculopathy in RCD and Usher Syndrome Patients



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Table 2. Treatment outcomes for Alternate day vs Every Day treatment

Intervention	Eyes n (%)	Patients n (%)	Mean reduction in OCT CMT/eye μm (%95 CI)	Mean reduction in Macular Volume/eye mm3 (%95 CI)	Follow up time, mo Median (range)	Subjective Vision improvement n patients (%)
Treatment 1	Brinzolamide 1% tds Alternate days					
	54	28				
Response	30 (55.5)	14(50)	105(82,128)	1.1 (0.5,1.9)	31.07 (6-48)	10 (71.4%)
No Response	24 (44.4)	14(50)	5(-15,10)	-1.2 (-1.5,-0.9)	22.51 (6-48)	0
Treatment 2	Brinzolamide 1% tds Every day					
	32	18				
Response	12 (37.5)	8 (38.8)	120 (52,178)	1.5 (0.8,1.8)	21.28 (6-48)	6 (75.0%)
No Response	20 (62.5)	10 (61.1)	9 (-3,11)	0.1 (-0.7,0.5)	23.87 (6-48)	0

Table 3. Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	Pr > ChiSq
Objective Vision (≥ 7 letters)			
Age	1.04	0.97 1.116	0.2679
Gender M vs F	0.359	0.052 2.47	0.2981
Treatment Trt1 vs Trt2	12.657	1.092 146.662	0.0423
Diagnosis ARRP vs ADRP	31.253	2.083 468.851	0.0127
Central Macular Thickness			
Age	0.981	0.945 1.018	0.3152
Gender M vs F	0.73	0.179 2.979	0.661
Treatment Trt1 vs Trt2	1.105	0.268 4.551	0.8901
Diagnosis ARRP vs ADRP	4.193	1.001 17.558	0.0498
Cyst Size reduction			
Age	0.963	0.923 1.004	0.076
Gender M vs F	1.676	0.384 7.302	0.4919
Treatment Trt1 vs Trt2	1.238	0.274 5.586	0.7816
Diagnosis ARRP vs ADRP	1.758	0.407 7.594	0.4498
Subjective Vision improvement			
Age	0.949	0.906 0.994	0.0263
Gender M vs F	1.719	0.408 7.24	0.4602
Treatment Trt1 vs Trt2	0.589	0.123 2.81	0.5067
Diagnosis ARRP vs ADRP	0.916	0.214 3.916	0.906
Any decrease in Macular Volume			
Age	0.995	0.957 1.034	0.7858
Gender M vs F	0.602	0.136 2.67	0.504
Treatment Trt1 vs Trt2	1.465	0.32 6.714	0.6227
Diagnosis ARRP vs ADRP	2.225	0.481 10.293	0.3062

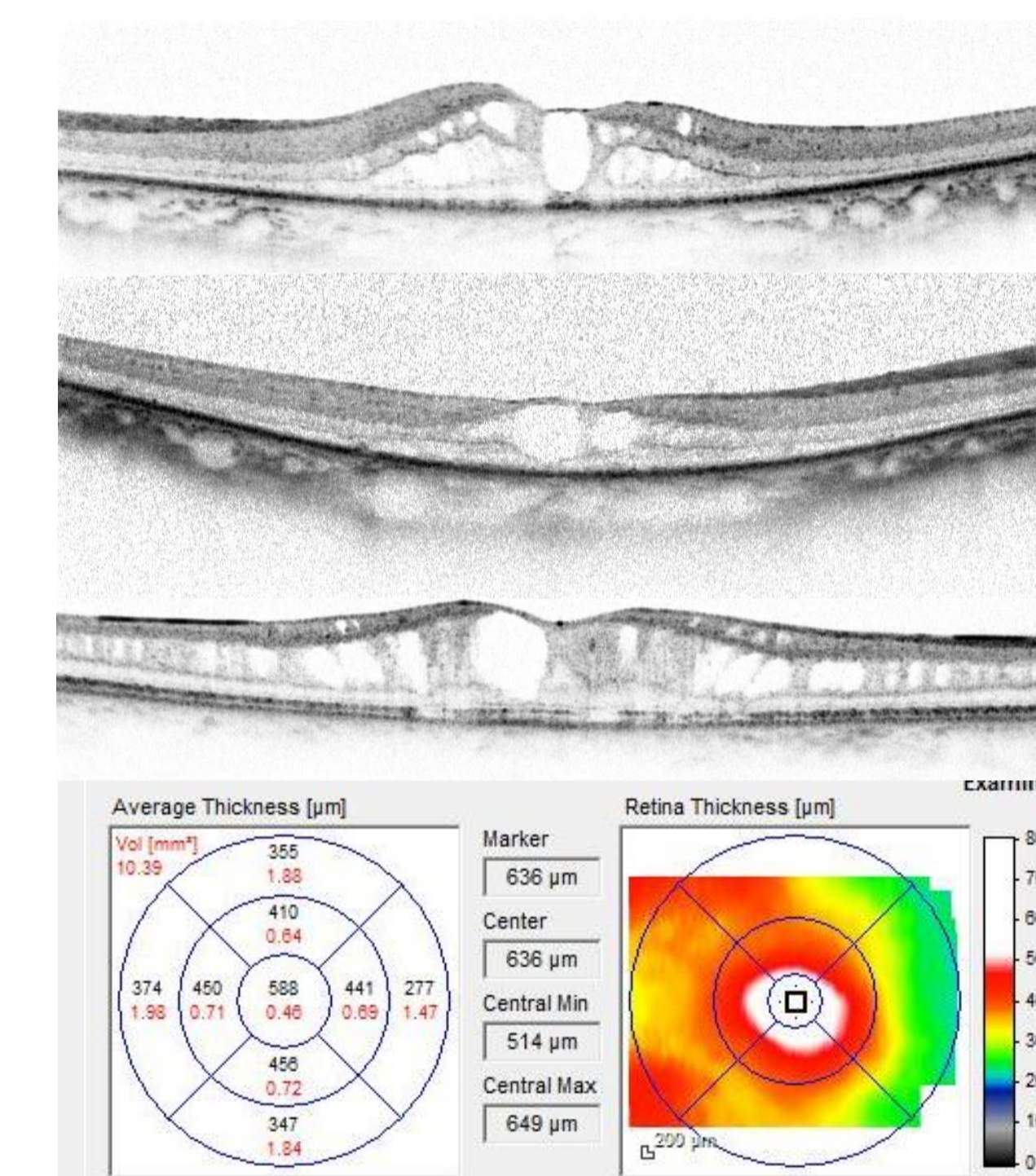


Figure 2. Cystic Maculopathy and CMT, and MV in RCD

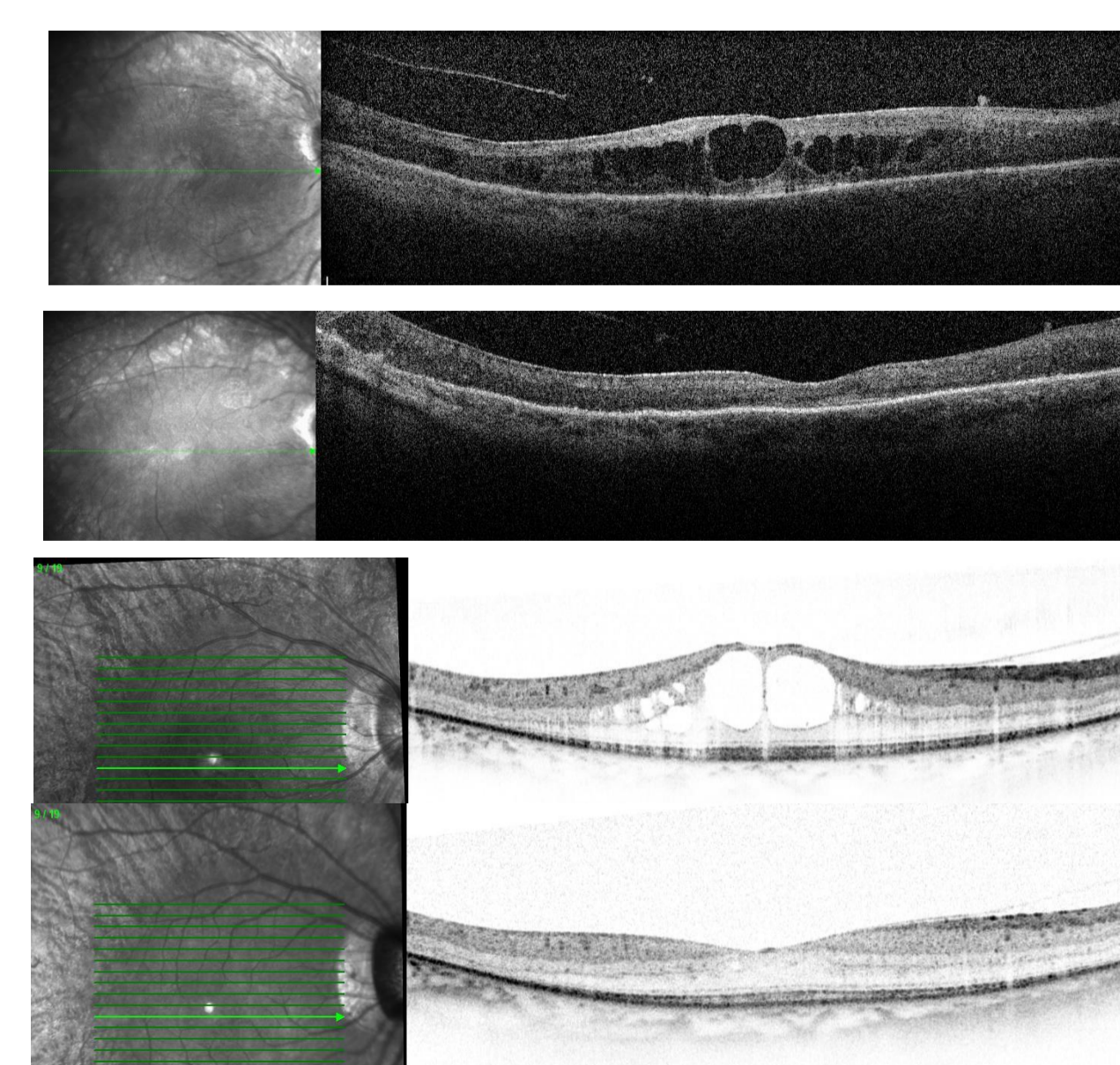


Figure 3. Response to topical brinzolamide in 2 eyes – NR2E3 above, EYS below

Results; Of 256 patients with RCD identified, 62 (24%) had CM, present in 40% with autosomal dominant(AD), 24% with autosomal recessive (AR) , and absent in X-Linked RCD. Complete data was available for 28 patients (54 eyes) on alternate day regimen (Treatment 1) , and 18 patients (32 eyes) on continuous treatment (Treatment 2). Median treatment was 32 months (6-48).

Treatment 1: 55% showed any response : 71 % had subjective VA improvement, objective VA improvement 50%, mean reductions in CFT 105μm (95%CI 82-128), and MV 1.1mm³ (0.5-1.9)

Treatment 2: 37% showed any response – 75% had subjective VA improvement, 44% objective VA improvement , mean reductions in CMT 120μm (52-178), and MV of 1.5mm³ (0.8-1.8).

Alternate day treatment compared with continuous was associated with a significant effect (p=0.04) for Objective vision improvement, with odds ratio(OR) for VA improvement 12.7 (95% CI 1.1-146.7).

Regardless of which treatment, a diagnosis of ARRCD had a significant association with the outcomes of Objective vision improvement, (p=0.01), OR 31.25 (2.5-468.9), and with reduction in central macular thickness (p=0.05), OR 4.19 (1.00-17.56) compared with ADRCD.

Of patients with proven *PRPF31* RCD, 80% had CM.

No other significant associations were present, and groups were too small to determine specific genotype/ treatment outcome significance.

Conclusion: CM associated with inherited RCD affects 25% of patients, and is more frequent in AD disease, but a larger treatment response to topical brinzolamide observed in AR disease. Alternate day dosing is more effective than continuous in CMT reduction, and objective VA improvement. Subjective improvement was greater than objective vision improvement in both groups, suggesting other parameters such as contrast sensitivity may be improved. Alternate day dosing with brinzolamide works more effectively than continuous dosing with less rebound, and may be due to RPE pump recovery.