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THE POTENTIAL ROLE OF RHO KINASE INHIBITORS IN OCULAR GRAFT vs HOST DISEASE

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INTRODUCTION

- Patients who undergo hematopoietic stem cell transplants(HSCT) are at risk for developing Graft vs Host Disease (GVHD) and its ocular manifestation (oGVHD)
- oGVHD is a severe dry eye disease
- Treatments for oGVHD are **limited** and tend to be **inadequate** in achieving remission.
- **Belumosudil**
- **Reduces inflammation** by decreasing ROCK2-induced STAT3 activity, which upregulates pro-inflammatory T helper 17 and follicular helper cells.[1]
- **Decreases fibrosis** by preventing actin polymerization and profibrotic gene transcription.[1]
- ROCK2 is expressed by corneal epithelial cells, suggesting Belumosudil's potential use for targeted oGVHD treatment.

PURPOSE

We hypothesize that patients on Belumosudil will have a **clinically meaningful improvement** in their oGVHD and will have a correlative improvement in their **tear cytokine profile.**

METHOD

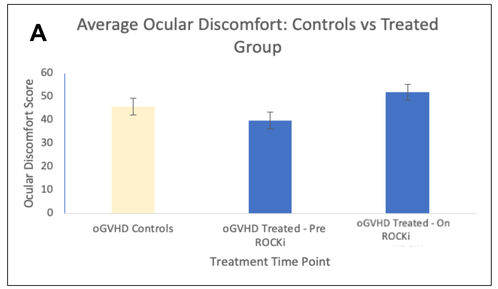
The study protocol was approved by the University of Maryland Institutional Review Board.

- Retrospective chart review of **3 patients** who received treatment for oGVHD at the University of Maryland Medical Center and **matched oGVHD non-treated controls**
- Data collected: **Ocular Surface Disease Index (OSDI)**, tear production via the **Schirmer's Test**, and pain with the **Ocular Discomfort Scale**.
- Cytokine tear analysis was performed with the **Luminex assay** to correlate changes with clinical findings[2,3]

RESULTS

Table 1: Demographics of treated oGVHD patients and matched oGVHD patients who were not treated with Belmuosudil but followed at UMMC. ROCKi = ROCK 2 inhibitor, Belumosudil

Patient	Sex	Age	Dx	Transplant	Donor Match
oGVHD	M	57	CML	MRD AlloPBSCT	Full match 10/10
oGVHD	F	65	CML	MUD AlloSCT	Full match 10/10
oGVHD	F	76	MDS	MUD AlloSCT	Full match 10/10
oGVHD+ Belumosudil	M	41	PMF	MRD AlloPBSCT	Full match 10/10
oGVHD+ Belumosudil	F	46	MDS	MUD AlloSCT	Full match 10/10
oGVHD+ Belumosudil	M	65	MDS	MRD AlloSCT	HLA matched, minor ABO mismatch



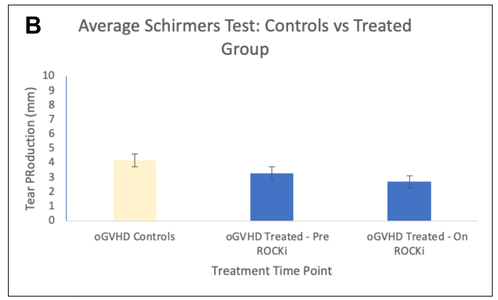


Figure 3: oGVHD group treated with Belmusodil versus oGVHD non-treated group.
3A. OSDI Score. No statistical difference between groups and between treatment status in Belmusodil treated group.

3B: Schirmers Score. No statistical between groups and between treatment status in Belmusodil treated group.

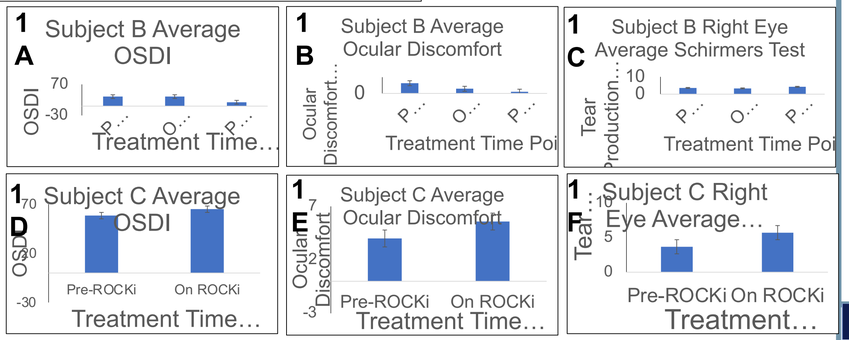


Figure 1. Subject B (A-C). Mean data from pre-, on, and post-treatment time periods, respectively, ±st dev with 95% confidence level. (A) Ocular surface disease index score of 30.54±18.07, 30.59±8.76, and 12.5±7.08. **p=0.0066** (B) Average ocular discomfort 4.4±1.33, 2 ±1.21, 0.75±0.69. (C) Right eye average Schirmers Test 3.6± 0.48mm, 3.33±0.67mm, 4.2±3.95 mm.
Subject C (D-F). (D) Ocular surface disease index 58.41± 8.75 and 64.93± 6.17; p=0.101.(E) Ocular discomfort score of 5.58± 1.38. (F) Right eye average Schirmers Test 3.67± 3.46 mm and 5.71±2.99 mm; p=0.8342.

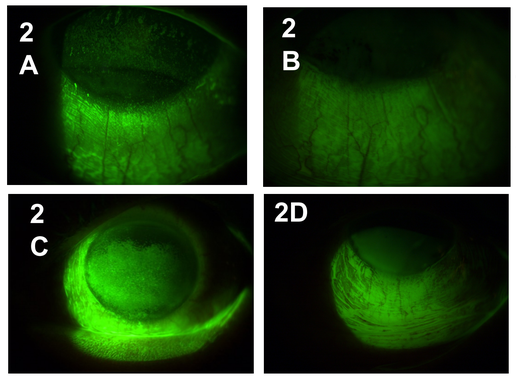


Figure 2. Subject B (2A/2B) Slit lamp photo of right eye, (**(2A)** pre-treatment. (2B)11 months after starting Belmusodil **Subject C (2C/2D).** Slit lamp photo of right eye (C) Pretreatment. (D) 6 months after starting Belmusodil.

Subject	MIP-1A	MIP-1B
A	45.84	57.02
B	2.66	1.08
C	11.48	5.32
Standard Deviation	22.81	31.15

Table 2: Tear Cytokine levels of patients treated with Belmusodil. The Luminex assay measured presence of macrophage inflammatory protein MIP-1A and MIP-1B in tear samples. An **inverse relationship** between length of treatment and levels of MIP -1alpha and MIP-1beta was observed. Patients who were treated by Belumosudil for a longer period had lower MIP -1alpha and MIP-1beta

CONCLUSIONS

- No statistically significant difference between oGVHD patients treated with Belumosudil compared to matched oGVHD patients
- There was **some individual improvement** during Belumosudil treatment

Our results suggest that Belumosudil may help the eyes of patients with oGVHD by lessening symptoms

Limitations:
- Small sample size
- Insurance coverage as a barrier to initiating treatment
- Selection bias of treated oGVHD patients based on severity status

Next Steps:
Larger cohort study and/or **prospective** investigation.

REFERENCES

1. Jagasia, Madan, et al. "ROCK2 inhibition with belumosudil (KD025) for the treatment of chronic graft-versus-host disease." Journal of Clinical Oncology 39.17 (2021): 1888. 2. Hagan, Suzanne, and Alan Tomlinson. "Tear fluid biomarker profiling: a review of multiplex bead analysis." The ocular surface 11, no. 4 (2013): 219-235. 3. Platchek, Michael, Quinn Lu, Hoang Tran, and Wensheng Xie. "Comparative analysis of multiple immunoassays for cytokine profiling in drug discovery." SLAS DISCOVERY: Advancing the Science of Drug Discovery 25, no. 10 (2020): 1197-1213.

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