cAMP-modulated Disease in MAGIS Syndrome

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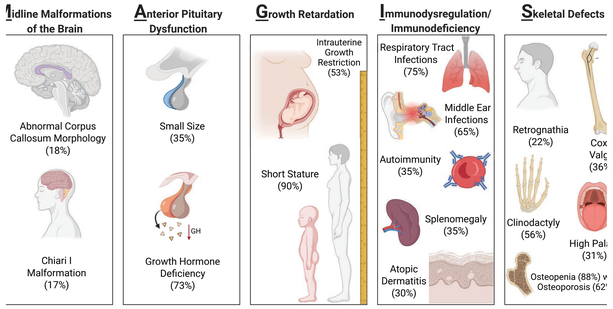
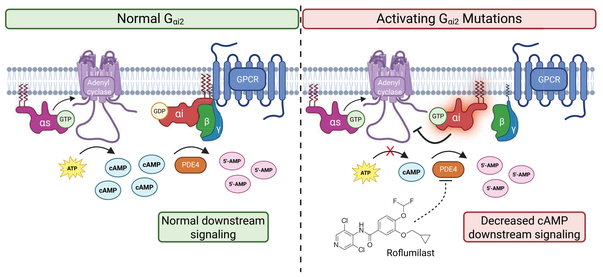
INTRODUCTION

G protein coupled receptors (GPCRs) are heterotrimeric protein complexes (composed of α, β, and γ subunits) that mediate cellular responses to a variety of environmental cues. Of the G_{α} subunits, the $G_{\alpha i/o}$ family contains inhibitory isoforms of the G_{α} subunit that have been shown to inhibit andenyl cyclase's production of the secondary messenger cyclic adenosine monophosphate (cAMP). Our lab has recently shown that activating mutations in $G_{\alpha i2}$, encoded by *GNAI2*, suppress production of cAMP and develop MAGIS syndrome (defined by **M**idline Malformations of the brain, **A**nterior hypopituitarism, **G**rowth retardation, **I**mmunodeficiency /immunodysregulation, and **S**keletal abnormalities (Ham H, e*t. al. Science,* 2024).



METHODS

Since phosphodiesterase-4 (PDE-4) inhibitors such as Roflumilast reduce cAMP breakdown, we hypothesized that treatment to increase cAMP levels might improve disease. We explored this possibility in a 36-year-old woman with MAGIS syndrome whose disease manifests in recurrent infections, autoimmunity, and increased inflammation , as demonstrated by leukocytosis in the setting of enteropathic arthritis [characterized by tenosynovitis in multiple joints in the setting of chronic colitis]. Additionally, she has Type 1 Diabetes Mellitus, as well as severe mixed hyperlipidemia and hypertriglyceridemia, possibly related to her growth hormone deficiency. These symptoms were closely monitored to elucidate the effect of increased cAMP on MAGIS syndrome.



RESULTS

Figure 1: Patient course of treatment from August 2023 to December 2024, during which Roflumilast treatment is initiated.

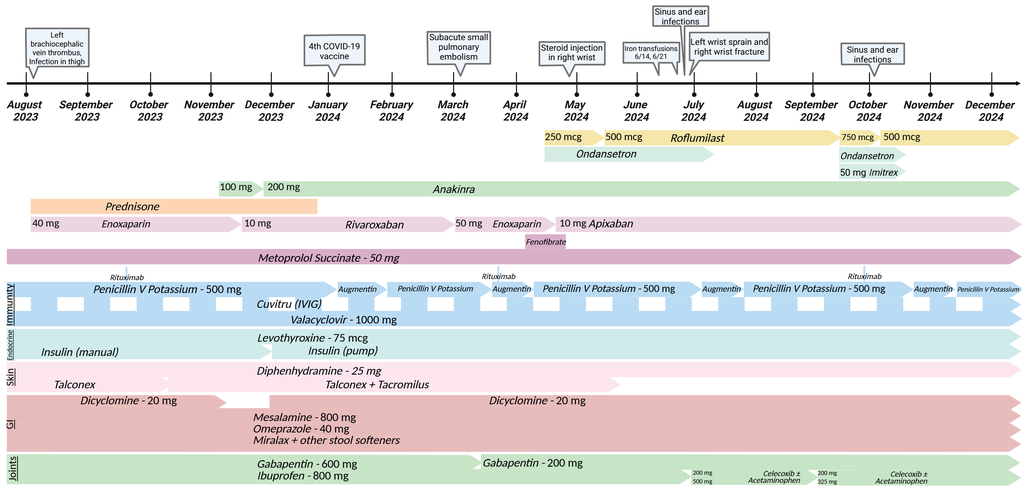


Figure 2: Left achilles ultrasounds show decreased tenosynovitis as Roflumilast treatment continues.

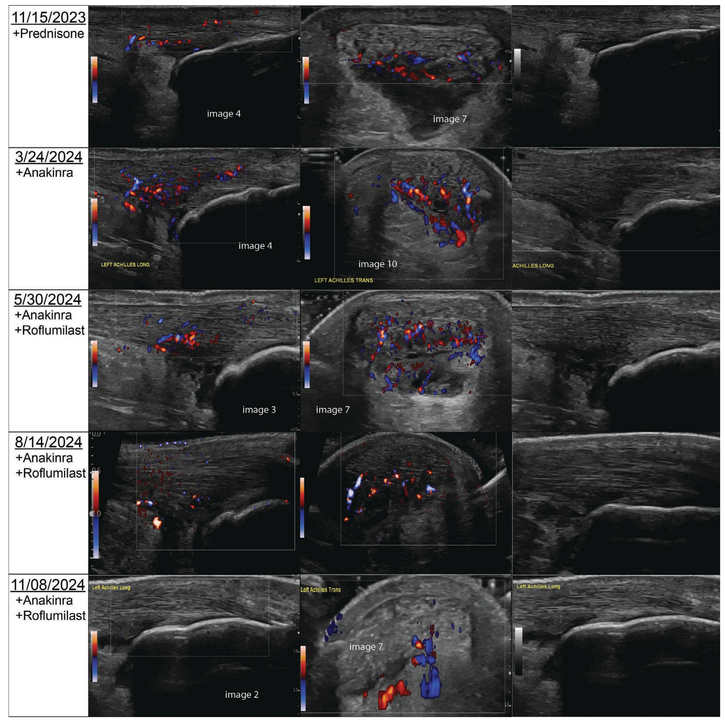


Figure 3: Pathology sections from patient's ascending colon show a reduction of active colitis after starting Roflumilast treatment.

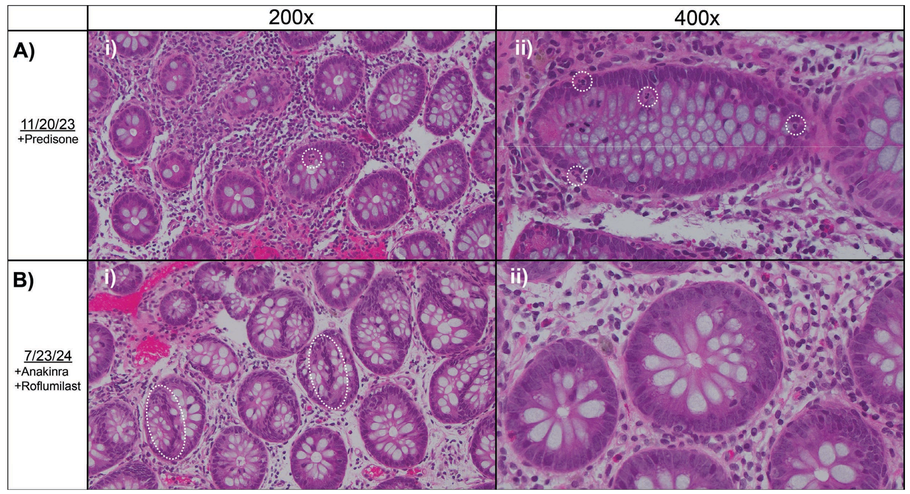
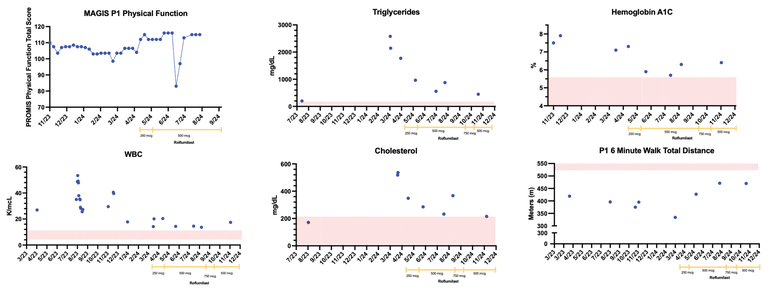


Figure 4: Routine metrics show improved physical function, leukocytosis, hyperlipidemia, Hemoglobin A1c and 6-Minute Walk after Roflumilast treatment.



CONCLUSION

After starting Roflumilast, weekly scoring using the Patient-Reported Outcomes Measurement Information System (PROMIS) showed increased physical function. This was consistent with the patient's self-report of decreased joint pain and objective measures of improved joint and tendon disease as documented by sequential ultrasounds. Leukocytosis normalized and histological findings from sequential colonoscopies showed decreased active colitis. Additionally, her triglyceride, cholesterol, and Hemoglobin A1C levels improved. These observations suggest that the suppressed cAMP might contribute to inflammatory disease in MAGIS, and if so targeted therapy to normalize cAMP might be beneficial in some patients.

FUTURE EXPERIMENTS

Moving forward, I plan to conduct *in vitro* assays with patient peripheral blood to assess whether Roflumilast treatment causes a reduction in pro-inflammatory cytokine production.

ACKNOWLEDGEMENTS

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