Combined MSC-antiviral treatment for systemic inflammation and lymphoid tissue regeneration in cats with FIP

Rachel Formaker, Patrawin Wanakumjorn, Diego Castillo, Amir Kol

Department of Pathology, Microbiology, and Immunology, UC Davis School of Veterinary Medicine

UC DAVIS VETERINARY MEDICINE
Students Training in Advanced Research

Background

- **Feline infectious peritonitis (FIP)** is a highly fatal disease of young cats caused by mutations in feline enteric coronavirus and an aberrant host immune response[1]. FIP causes multi-system pyogranulomatous inflammation and lymphoid tissue injury[1].
  - **Nucleoside analog GS-441524** is an antiviral that effectively treats FIP in ~80% of cases[2]. However, its effects on immune system recovery have not been explored.
- **Multipotent stromal cells (MSCs)** have immunomodulatory properties; they promote tissue regeneration and reduce immune hyperreactivity when administered therapeutically[3].
  - Allogeneic MSCs have successfully and safely treated refractory feline chronic gingivostomatitis (FCGS)[4].
  - MSCs increased survival, reduced pro-inflammatory cytokines, and increased lung tissue regeneration in patients with COVID-19[5], demonstrating efficacy in viral inflammatory disease.

Hypothesis & Aims

Hypothesis: Addition of MSCs to antiviral therapy will modulate systemic inflammation and facilitate lymphoid tissue regeneration in cats with feline infectious peritonitis (FIP).

- Aim 1: Determine the impact of combined GS-441524-MSC treatment on systemic inflammation in cats with FIP
- Aim 2: Determine the impact of combined GS-441524-MSC treatment on peripheral blood lymphocyte counts in cats with FIP

Methods

A randomized, double-blind, placebo-controlled trial with 10 client-owned cats with effusive FIP was performed.

- All cats received daily oral antiviral GS-441524 for 11 weeks.
- On weeks 1 and 3, cats received infusions of either MSCs (n=5) or saline (n=5).
- Blood samples were collected at weeks 0, 1, 3, 7, and 11.

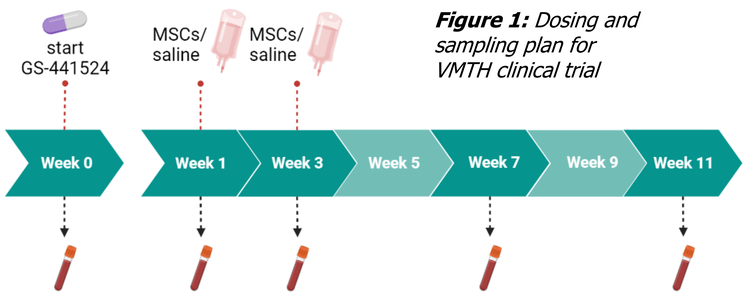

Figure 1: *Dosing and sampling plan for VMTH clinical trial*

Aim 1: Samples were assayed using the Milliplex Feline Cytokine/Chemokine Magnetic Bead Panel 19-Plex and read using a Luminex® analyzer.

Aim 2: Manual 400-cell differential leukocyte counts were performed. Total leukocyte counts were measured using the ADVIA 120 analyzer. Peripheral blood lymphocyte counts were calculated.

Results

Cytokine Quantification

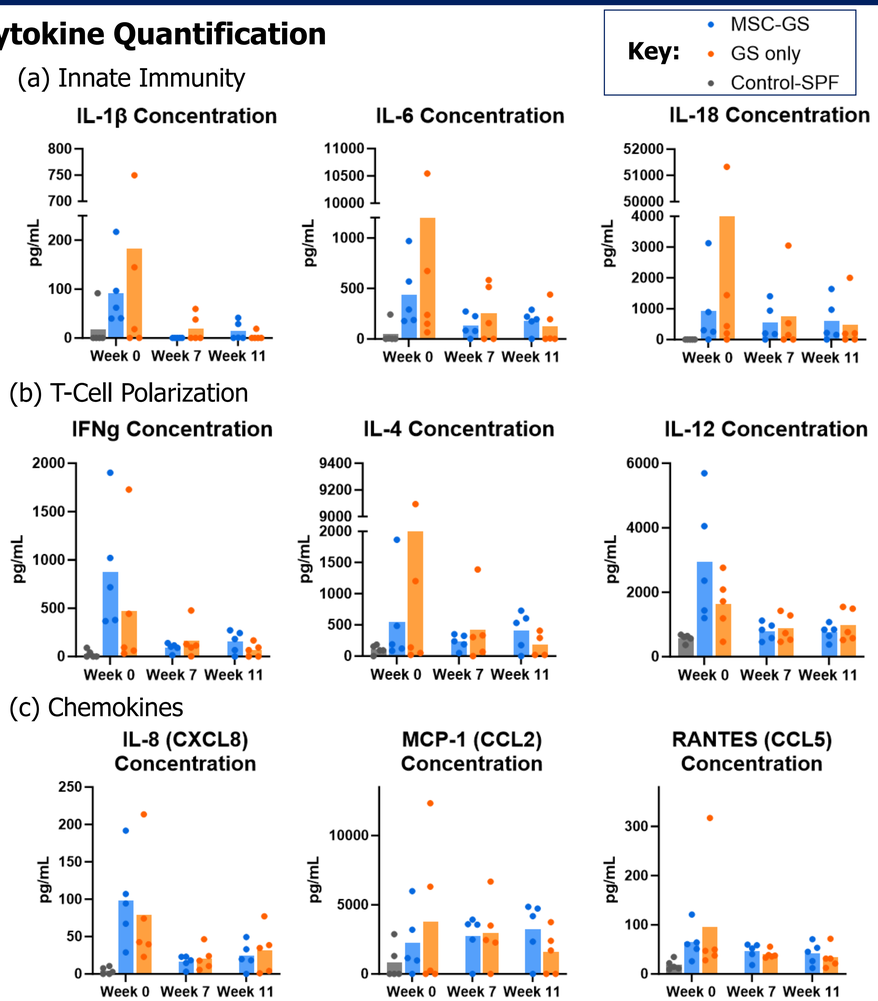

Figure 2: *Concentration over time of cytokines involved in innate immune response (a), T-cell polarization/adaptive immunity (b), and chemokines (c) in cats with FIP and healthy controls*

Lymphocyte Quantification

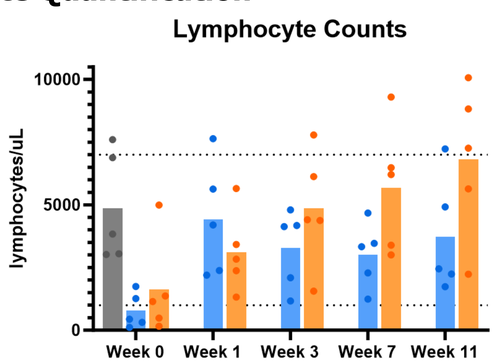

Figure 3: *Concentration over time of peripheral blood lymphocytes in cats with FIP and healthy controls*

Discussion

- **MSC therapy was safe with no adverse events reported.**
  - Previously reported risks of increased thrombosis with MSC therapy; not seen here
- Compared to controls, **cats with FIP presented with higher levels of many pro-inflammatory cytokines and chemokines**.
- Cats in **both treatment groups show decreasing levels of these cytokines and chemokines over time with treatment.**
  - FIP cats appear to have higher than control levels of many cytokines and chemokines even after 11 weeks of treatment and clinical remission.
- **50% of cats presented with lymphopenia, and 90% presented with either low or low-normal levels of lymphocytes.**
  - Lymphopenia resolved by the week 1 visit, at which point cats have only received GS-441524.
  - Cats in the MSC group have more consistently normal levels of lymphocytes during treatment, while the GS only group appears to trend toward a lymphocytosis, indicating potential immunomodulation by the MSCs.
- **No apparent difference between treatment groups**

Future Directions

- Correlation of cytokine patterns and hematologic results
- Addition of MSCs to antiviral therapy in **non-effusive FIP**
  - Non-effusive FIP is harder to successfully treat with antivirals alone, and therefore creates a need for further treatment as well as an opportunity to explore the effects of MSCs.

Acknowledgements

Financial support was provided by the UC Davis SVM Students Training in Advanced Research (STAR) Program, NIH T35 Training Grant 5T35OD010956-24, and NIH/NICHD Grant R21HD106027-01.

References

[1]Pedersen, N. C. An update on feline infectious peritonitis: virology and immunopathogenesis. *Vet. J.* **201**, 123–132 (2014).
[2]Murphy, B. G. *et al.* The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies. *Vet. Microbiol.* **219**, 226–233 (2018).
[3]Singer, N. G. & Caplan, A. I. Mesenchymal stem cells: mechanisms of inflammation. *Annu. Rev. Pathol.* **6**, 457–478 (2011).
[4]Arzi, B. *et al.* Therapeutic efficacy of fresh, allogeneic mesenchymal stem cells for severe refractory feline chronic gingivostomatitis. *Stem Cells Transl. Med.* **6**, 1710–1722 (2017).
[5]Shi, L. *et al.* Mesenchymal stem cell therapy for severe COVID-19. *Signal Transduct. Target. Ther.* **6**, 339 (2021).
Figure 1 created using Biorender.com.
Figures 2-3 created using GraphPad Prism; www.graphpad.com.