Combined MSC-antiviral treatment for T cell injury in cats with spontaneous feline infectious peritonitis (FIP)

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Feline infectious peritonitis (FIP) is a common and lethal disease of cats caused by infection with an enteric coronavirus that mutates to infect macrophages and cause severe systemic inflammation.

Lymphocyte apoptosis and T cell exhaustion are suspected contributors to FIP pathogenesis, resulting in lymphopenia, lymphoid tissue atrophy, and further disease progression.

GS-441524 is an experimental antiviral that has successfully treated FIP. However, its ability to regenerate damaged lymphoid tissue and restore normal immune function post-infection is unknown.

Multipotent stromal cells (MSCs) have immunomodulatory and regenerative properties. We are interested in exploring the use of MSCs as a combined therapeutic with GS-441524 in order to support long-term recovery from FIP.

Hypothesis: FIP induces T cell injury that results in cell loss and exhaustion, and a combined MSC-antiviral therapy will support restoration of depleted lymphocyte populations and rejuvenation of exhausted T cells to a greater extent than antiviral therapy alone.

Aim #1: Determine lymphocyte subset proportions (B, T, CD4, CD8) upon presentation and over the course of treatment.

Aim #2: Determine the frequency of polyfunctional T cells upon presentation and over the course of treatment.

Methods (continued)

Double-blinded and randomized clinical trial with 10 client-owned cats with effusive FIP.

• Treatment groups (each n=5)
  1) Combined antiviral-MSC
  2) Antiviral-saline (placebo)

• All cats received GS-441524 PO daily for 11 weeks

• MSC/placebo infusions administered at weeks 1 and 3

• Blood collected at weeks 0, 1, 3, 7, 11

• 5 cats from a specific pathogen free (SPF) colony as healthy controls

Results (continued)

No apparent difference in CD4+ or CD8+ proportions between healthy and FIP cats upon presentation.

Both treatment groups showed an upward trend in CD8+ proportions over time.

Future directions:

• Continue data analysis
  • Correlation of flow results with hematology, cytokine, and clinical data
  • Acquire data for remaining 3 FIP and 2 SPF cats
  • Panel 3: exhaustion markers
    • L/D, CD5, CD4, CD8, CTLA-4, EOMES, FAS, TOX

Discussion

• Completed Panels 1 and 2: 7 FIP cats (3 MSC, 4 saline) and 3 SPF cats
• Some data points not viable
• Cats with FIP have a markedly increased proportion of events within the lymphocyte gate that are both CD5+ and CD21+ upon presentation.
• Cats with FIP have highly variable CD5+/CD21+ ratios upon presentation, some of which are markedly increased compared to healthy controls.
• Cats with FIP have increased variability in CD4+/CD8+ ratios upon presentation and over the course of both treatments.
• No apparent difference in CD4+ or CD8+ proportions between healthy and FIP cats upon presentation.
• No apparent difference in CD4+ proportions following both treatments.
• Both treatment groups showed an upward trend in CD8+ proportions over time.

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References

Figure 1. Preparation process of blood samples for flow cytometry

Figure 2. FlowJo gating strategy for Panel 1 (surface markers)

Figure 3. FlowJo gating strategy for Panel 2 (intracellular cytokines)

Figure 4. (a) Lymphocyte subset proportions and (b) cytokine production levels over time