Scoping review of the use of mesenchymal stem and stromal cell products in cats, Part 2: current scope and efficacy

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ABSTRACT
A scoping review of published literature found 108 articles related to mesenchymal stem or stromal cell (MSC) use in cats. Twenty-four of the publications summarized the treatment of 192 cats with MSC products for 12 naturally occurring and induced diseases. These trials used a variety of cell sources, administration routes, delivery vehicles, and dosages. The majority of studies did not have a control group. The disease with the largest number of cats administered MSCs thus far is chronic kidney disease (n = 59 cats). The majority of cats had no adverse events associated with treatment, which supports continued interest in the potential use of MSC products to address unmet medical needs. Treatment outcomes of the 192 cats have ranged from no response to long-term cure, depending on the disease being treated and the particular study. Some of these early studies show promise and provide significant information to direct both the design and focus of larger clinical trials investigating the safety and efficacy of MSC treatment for veterinary and human applications.

Keywords: stem cell, stromal cell, feline, mesenchymal, efficacy

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ignificant interest has been placed on the potential of mesenchymal stem cells (MSCs) and related animal cell and tissue-based products (ACTPs) to address unmet therapeutic needs in veterinary and human medicine. Despite the promise and the significant number of feline diseases without effective treatments, there are currently no approved veterinary stem cell products available for use in cats in the US.

The companion review to this article noted that the published literature includes information on only 215 cats treated with MSCs and MSC products to date.1 Only 12 of the 26 (46.2%) published studies describing the administration of MSC products to cats included a control group, and these experimental and clinical trials used 7 cell sources, 9 administration routes, 12 delivery vehicles, and a 300-fold range in dosages for pilot studies in healthy cats and cats with naturally occurring and induced diseases.1 Although publications about feline MSCs have increased over the past 10 years, the wide variety and small number of studies using MSCs and MSC products in cats demonstrate that current evaluations are mostly still in the discovery phase.1

To understand the current status of MSCs and MSC product use in cats, a scoping review of the published literature to date was performed. A review of study logistics and safety was published separately.1 This article summarizes the currently available literature on the use of MSCs and MSC-related products in cats with a focus on current scope and efficacy to provide guidance for clinical study recommendations and future research efforts.

Methods
An online bibliographic database (PUBMED) was searched in January 2024 for relevant publications of sufficient detail for analysis. The bibliographies of identified studies were further evaluated for relevance. Additional keyword searches were performed in PUBMED and Google Scholar for cross-reference and validation. Study information was summarized for review and descriptive analysis using Microsoft Excel and GraphPad Prism 10.

Results
Available articles
PUBMED search terms included ((feline) AND ((stem cell) OR (stromal cell) OR (stromal vascular
fraction))), which resulted in 1,664 articles. A filter was applied to limit dates from 2002 to 2024 based on the date of the first publication describing feline MSCs. Articles were individually reviewed for relevance as described in a previous article.

Twenty-six articles were identified that described primary administration of MSCs or MSC products to cats in experimental and clinical studies. Of these 26 publications, 2 studies were in healthy cats and excluded from this review. Fourteen of the 24 (58.3%) publications were studies in cats with naturally occurring disease, 8 (8/24 [33.3%]) were studies in induced models of disease, and 2 were single case studies for a total of 192 treated cats. One retrospective study reported on long-term follow-up on some of the cats included in the previous 24 articles; this study was not included in the results due to overlap with previous articles.

Eleven of the 24 (45.8%) publications describing primary administration of MSCs or MSC products to cats with disease included a control group (Figure 1). The number of cats treated per publication ranged from 1 to 24, with a median of 5 cats. Cats were treated with a median of 2 doses (range, 1 to 6). The majority of cats were treated with allogeneic cells (117/168 [69.6%] cats; Figure 2); information on donor type was not available for 1 study accounting for 24 cats. The majority of MSC products were delivered IV (136/192 [70.8%] cats). The overall rate of adverse events, defined as any untoward medical occurrence associated with the use of a drug whether or not considered drug-related, was up to 22.4% (43/192 cats) as inferred from the publications; in studies that did not state the number of cats that experienced adverse events, the adverse events were counted as occurring individually. Up to 18 cats with naturally occurring disease (18/112 [16.1%] cats) and 25 cats with induced disease (25/80 [31.3%] cats) had reported adverse events.

Diseases

Cats with 12 different diseases were treated with MSCs or MSC products in the reviewed publications (Figure 3). Six of the diseases were naturally occurring including 112 of the 192 (58.3%) treated cats, and 6 of the diseases were induced including 80 of the 192 (41.7%) treated cats. Naturally occurring chronic kidney disease (CKD) and refractory feline chronic gingivostomatitis (FCGS) were the focus of the majority of publications (5 each; Figure 1) and also included the most cats treated, with 41 (21.4%) and 45 (23.4%) of the 192 treated cats, respectively. Two related publications evaluated the use of MSCs in naturally occurring chronic enteropathy (10/192 [5.2%] treated cats) and inflammatory bowel disease (IBD; 6/192 [3.1%]). One publication each evaluated MSC use in naturally occurring eosinophilic keratitis (5/192 [2.6%] treated cats) and chronic spinal cord injury (3/192 [1.6%]). The 2 case reports evaluated...
MSC use with implants in a large osseous defect in the tarsus\textsuperscript{26} and a chronic oronasal defect.\textsuperscript{25}

Studies involving induced disease in cats included 2 each on models of acute kidney injury (AKI; 13/192 [6.8%] treated cats),\textsuperscript{21,22} allergic asthma (9/192 [4.7%]),\textsuperscript{17,20} and chronic spinal cord injury refractory to standard treatment and rehabilitation for at least 2 months. The cats were followed for 90 days, and no adverse events were reported. There was no control group. The authors\textsuperscript{14} reported that treatment combined with physical rehabilitation led to restoration of weight-bearing locomotor function and spinal reflexes, although these improvements diminished after 45 days.

Hemorrhage—Two independent case studies\textsuperscript{25,26} reported on the use of MSCs and bone marrow on implants used to treat osseous defects. The first case used autologous platelet-rich plasma and uncultured bone marrow aspirates with 3-D–printed polycaprolactone scaffold for treatment of a chronic oronasal defect.\textsuperscript{25} Although the implant was not observed and limited bone healing was noted on CT scan 2.5 months postoperatively, the cat was followed for 10 months with no adverse events, and good wound healing and improved quality of life were reported. The second case study\textsuperscript{26} described the treatment of an infected
Allergic asthma—Two randomized, controlled studies investigated MSCs in an induced model of feline allergic asthma. Allogeneic adipose-derived MSCs were shipped to the study site and included both cryopreserved and freshly cultured cells in a range of doses given IV 6 times in the initial study and 5 times in the second study. In the first study, 5 cats were followed for 12 months and no decrease in airway inflammation was observed; however, MSC treatment temporarily decreased airway remodeling as measured using CT-derived inspiratory global bronchial wall thickness and global lung attenuation scores. The 4 cats in the second study were followed for 9 months and showed possible delayed reduction in airway inflammation, hyperresponsiveness, and remodeling. The only reported adverse event was the development of a scrotal sarcoma in 1 cat 1 month poststudy.

Multiple sclerosis—A single study evaluated the effects of a single intrathecal injection of 10 X 10^6 laser-activated, fresh nucleated cells in SVF from autologous adipose tissue in 5 cats with induced multiple sclerosis. The study was placebo controlled, and the cats were followed for 28 days. Adverse events were not reported. SVF treatment resulted in improved locomotion, remyelination, and regeneration capacity, decreased lesion extent and intensity, and reduced apoptosis and axonal regeneration.

Cardiomyopathy—A single study evaluated the therapeutic benefit of a single intracoronary injection of 1 X 10^6 autologous CD117+ isolated cardiac-derived stem cells in 7 cats and bone marrow–derived MSCs in 4 cats after injury in isoproterenol-induced cardiomyopathy. The study was placebo controlled, and the cats were followed for 66 days with no reported adverse events. Although both cell types improved cardiac function and attenuated pathological remodeling, MSCs appeared to confer additional benefits, and the authors concluded that MSCs may be the optimal source of stem cells to treat cardiac disease.

Traumatic optic neuropathy—A single study evaluated whether intravitreal injection of bone marrow–derived MSCs could increase survival of retinal ganglion cells after induced traumatic optic neuropathy in 24 cats. The study was placebo controlled, and the cats were followed for 28 days with no reported adverse events. MSC transplantation was found to slow apoptosis of retinal ganglion cells and thereby mediate neuroprotection after optic nerve injury potentially mediated by secretion of brain-derived neurotrophic factor.

Discussion

To date, 24 publications are available that describe experimental and clinical trials administering MSCs and MSC products to a total of 192 cats with naturally occurring or induced disease. These trials used 6 cell sources, 8 administration routes, 11 delivery vehicles, and a 300-fold range of dosages. The majority of studies did not have a control group and used 2 doses of allogeneic adipose-derived MSCs IV in a median of 5 cats and monitored them for a median duration of 136 days (approx 4.5 months). The majority of cats (149/192 [77.6%] treated cats) had no reported adverse events associated with treatment, which supports continued interest in the use of MSC products as potential therapies for unmet medical needs. However, the accuracy of adverse event information is dependent on the patient numbers, monitoring, and follow-up performed and information reported in the available publications. Further information on types of adverse events is included in the companion review paper. Treatment outcomes of the 192 cats with 12 diseases in the 24 reviewed publications ranged from no response to long-term cure, depending on the disease being treated and the particular study.

ACTPs, such as MSCs, are classified as drugs by the FDA. Accordingly, MSC products must be approved by the FDA to be used outside of clinical trials based on demonstration of safety and efficacy data, and clinical trials using ACTPs in client-owned animals must be included in investigational files opened with FDA before study initiation. Efficacy can be described simply as inducing a desired result, and there is no particular level of efficacy required under US law for FDA approval. However, demonstration of efficacy for drug approval generally involves “meeting the substantial evidence standard” based on adequate and well-controlled clinical investigations and confirmatory evidence for a specific product.

Are MSCs or MSC products effective to treat disease?

Current literature supports that MSCs and MSC products show promise in treating certain cats and diseases. However, the level of evidence for most diseases is very low due to low numbers of studies, small patient numbers, and lack of randomized, controlled trials. The most commonly studied diseases for application of MSC-based therapies in cats are CKD and refractory FCGS, and only 1 controlled clinical trial has been performed in a small number of cats with each disease. Both of these diseases lack effective therapies for a large number of affected cats. Overall, CKD is the disease with the most cats treated with MSCs thus far, with 59 cats over 6 studies (Figure 3). However, the wide variety of protocols, applications, and monitoring over a small number of cats make comparisons even within 1 disease challenging. Outcomes for CKD cats treated with MSCs have generally been less than...
desired, with some studies showing no benefit at all, including the controlled trial, and others showing modest improvement in some parameters. An important question is whether significant changes in values such as creatinine are clinically relevant to patient outcomes. Although no impact on mortality in CKD cats has been demonstrated, improvement in behavior has been reported.11,22

The most comparative data for MSC use in cats is available for refractory FCGS where many of the studies have been performed using the same protocol in the 45 treated cats summarized in the reviewed publications. The current available studies of cats with refractory FCGS treated with MSCs have shown marked improvement or complete, durable cure in the majority of cats, especially with autologous therapy. A recent retrospective study27 reported an overall positive response rate of 65.5%, with 58.6% of cats exhibiting long-lasting improvement or cure. Importantly, 91% of owners reported they would seek treatment with MSC again.27 Interestingly, a more recent clinical trial13 evaluated adipose-derived MSC in cats with FCGS before full-mouth tooth extractions and showed a lack of clinical efficacy. Some of the studies1,12,27 showed that clinical responses were correlated with potential biomarkers of disease severity including levels of CD8+ lymphocytes and cytokines, such as IL-6, IL-1β, and interferon-γ, among others. Although outside current normal clinical diagnostics, these findings provide information on MSC mechanism of action and a means of identifying cats that might respond to MSC therapy.32

The remaining diseases studied have very little currently available data to determine potential efficacy and many involved induced disease as preclinical studies for people. The 2 most promising, however, are feline enteropathy and refractory eosinophilic keratitis. Two studies5,15 are available treating cats for chronic enteropathy or IBD, both of which were blinded, randomized controlled trials. The first study5 was placebo controlled and showed improved clinical signs in 8 of 9 treated cats (1 of the 10 cats was lost to follow-up) with no reported adverse events. The follow-up study15 in cats with diagnosed IBD directly compared MSC therapy with standard-of-care treatment. Although the groups were small (6 cats each), similar improvement was seen in both groups with significantly improved feline chronic enteropathy activity index scores only in the MSC-treated group. Again, no adverse events were seen in MSC-treated cats.

The 1 study10 using allogeneic adipose-derived MSC subconjunctivally in 5 cats with refractory feline eosinophilic keratitis showed a 100% response rate by 6 months with no reported adverse events. Unfortunately, no follow-up studies have been published thus far. Several studies1,9,16,17,20,27 have similarly noted that response to MSC therapies in cats may take 6 months or longer to fully appear. Considering the median follow-up time in the current studies was 4.5 months, longer follow-up times should be considered in future investigations.

What MSC or MSC product is most effective?

With the small number of currently available studies and the large variability in study protocols, the most promising MSC or MSC product is not currently evident. Some potential differences in efficacy have been noted, such as an increased response rate in cats with refractory FCGS when autologous cells are used.27 However, the response rate has to be balanced with twice the incidence of adverse events, such as increased respiratory rate, fever, vomiting, and lethargy, even if mostly mild and transient.27 Autologous cells may carry less risk of infectious disease transfer but may have altered growth characteristics or function due to the presence of disease and the impact of concurrent medication administration.5,33,34 Additionally, the procedures required to collect tissues from sick cats may detract from any perceived benefit of using autologous cells.5,11

Few clinical studies have directly compared different cell types, doses, or administration characteristics in vivo. In 1 of the CKD studies,4 increased adverse events were seen with higher doses of cells taken directly from cryopreservation. Intrarenal or intra-arterial administration routes are more labor intensive and technically demanding than IV delivery.5,11 In FCGS, a recent study16 evaluated the use of placenta-derived MSCs as an alternative to adipose-derived MSCs and saw clinical improvement in all cats. Baring identification of significant differences in safety or outcome, the most easily available and resource-sparing options for MSC product generation and administration decrease donor, recipient, and care-giver burden as well cost of treatment, which can be significant in cell-based therapies. Continued in vitro studies evaluating cell characteristics, culture conditions, and mechanism of action can help identify the most promising treatment options and recipients before in vivo studies are performed.

Next steps

Combined with the increasing number of publications about feline MSC cell characterization and mechanism of action,1 the studies reviewed in this article provide valuable information to direct and optimize further clinical studies using MSC products in cats. As an example, IBD, kidney disease, and FCGS are currently listed as areas of interest or clinical trials by companies involved in veterinary regenerative medicine suggesting these applications are the most promising for product development. Recent conference proceedings related to the use of MSCs in cats also suggest additional ongoing clinical trials in refractory FCGS30 and feline infectious peritonitis for lymphoid tissue regeneration and effective antiviral immunity.35

This 2-part review provides current information on the use of MSC products in cats. Combined with knowledge of the current policies and regulations on the use of these products in client-owned animals,28,29,37–40 veterinary clinicians can use this information to help make informed recommendations to owners about the participation of their cats in clinical
trials using MSC products. Additional information and open clinical trials can be found by contacting researchers in the field and searching the AVMA’s Veterinary Clinical Trials Registry41 and the FDA Center for Veterinary Medicine Clinical Field Studies for Animal Cells, Tissues, and Cell- and Tissue-Based Products webpage.42 Informed, collaborative efforts between clinicians, researchers, regulators, and pet owners provide the best opportunity to design and complete quality, high-powered veterinary clinical trials that translate potential clinical solutions, such as MSC products, safely and effectively from the laboratory to the patient to address unmet therapeutic needs and improve health outcomes.

In conclusion, currently, 24 publications are available that summarize the treatment of 192 cats with 12 naturally occurring and induced diseases using MSC products. Treatment outcomes have ranged from no response to long-term cure, depending on the disease being treated and the particular study. Some of these early studies show promise and provide significant information to direct both the design and focus of larger clinical trials investigating the safety and efficacy of MSCs and MSC products for veterinary and human applications.

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