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Mesenchymal Stem Cells to treat Inflammatory Bowel Disease

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ABSTRACT

Inflammatory bowel disease (IBD) is a term for two chronic conditions. These diseases are Crohn's disease and ulcerative colitis that are both identified by inflammation in the gastrointestinal (GI) tract. Crohn's disease can occur anywhere in the digestive tract. In contrast to that, ulcerative colitis is limited to just the colon. Along with that, Crohn's disease can have gaps of healthy tissue in between inflamed areas while ulcerative colitis has no healthy gaps amongst inflamed areas. Factors such as stress and diet have been proven to aggravate symptoms of inflammatory bowel diseases. Symptoms include abdominal pain, fatigue, joint pain, and anemia. Crohn's disease and ulcerative colitis can cause ulcers, bowel obstruction, fistulas, malnutrition, and many other health conditions. There is also increased risk of cancer and blood clots. These factors make efficient treatments crucial for the disease. Researchers have tested stem cells and their efficiency to treat inflammatory bowel diseases. This is because stem cells are cells that have not become specialized. This allows for the cell to produce new cells or replaces specialized damaged or lost cells. Mesenchymal stem cells (MSCs) have been used in both human and animal research to treat inflammatory bowel disease. This type of stem cell can differentiate into various tissue types. Mesenchymal stem cells also contain anti-inflammatory and anti-fibrotic properties making it ideal to treat inflammation in autoimmune diseases. Mesenchymal stem cells have shown to be capable of treating inflammatory bowel disease due to their regenerative capabilities, immune-suppressive properties, and anti-inflammatory components. This has been seen in animal and human patients by achieving an increase in quality of life through results like reduced inflammation, complete remission, and reduced health complications making it an ideal treatment to continue and research for inflammatory bowel disease.

Keywords
Inflammatory Bowel Disease, Stem cells, Treatment.

Introduction

Approximately 3.1 million adults (1.3%) have been diagnosed with an inflammatory bowel disease (IBD) in the United States. Over 70,000 new cases of inflammatory bowel disease are diagnosed annually. This disease also affects more than 6 million people globally [1]. This disease is most diagnosed within the ages of 15 to 25 years old [2]. It also affects individuals from all different genetic backgrounds. An estimated 23-45% of patients diagnosed with ulcerative colitis require surgery at some point within their treatment. Along with this, 20% of ulcerative colitis patients are predicted to undergo a colectomy meaning the entire colon is surgically removed. Around 75% of Crohn's patients are predicted to undergo surgery as well [3]. If medication does not treat symptoms or achieve remission in the patient, surgery is considered to prevent further damage in the digestive tract.

The digestive system is one of the most vital systems due to its ability to convert food into nutrients and energy which is needed for survival. These nutrients include protein, fats, vitamins, minerals, carbohydrates, and liquids. Along with this, the digestive tract is responsible for 70% of human's immune system making it crucial to develop to fight infection [4,5]. In order, the digestive tract is composed of the mouth, esophagus, stomach, small intestine, large intestine, rectum, and anus [4]. Inflammation in the organs within the digestive tract leads to a loss of surface area.

The loss of normal surface area within the digestive tract has been shown to cause weight loss, anemia, inability to absorb nutrients correctly, decrease digestive enzymes, and a decreased overall breakdown of food sources [1,6]. Inflammatory bowel disease is directly associated with inflammation within the digestive tract. The inflammation can cause abdominal pain and server health complications over time especially if left untreated. These symptoms can be presented through flares or episodes.

A normal digestive tract is shown in the left figure and does not experience inflammation within the lining of the organs. The red shading in the middle figure indicates places where inflammation could occur for Crohn's disease. Crohn's disease inflammation is not limited to one area or organ. In contrast to this, the red shading in the right figure is limited to the colon for ulcerative colitis.

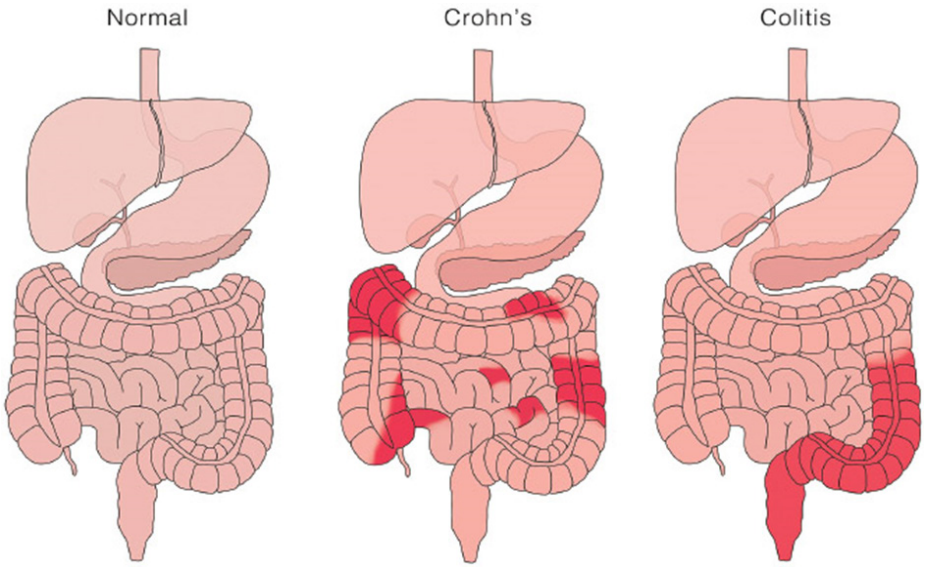

Figure 1: Inflammatory bowel disease symptom model [7].

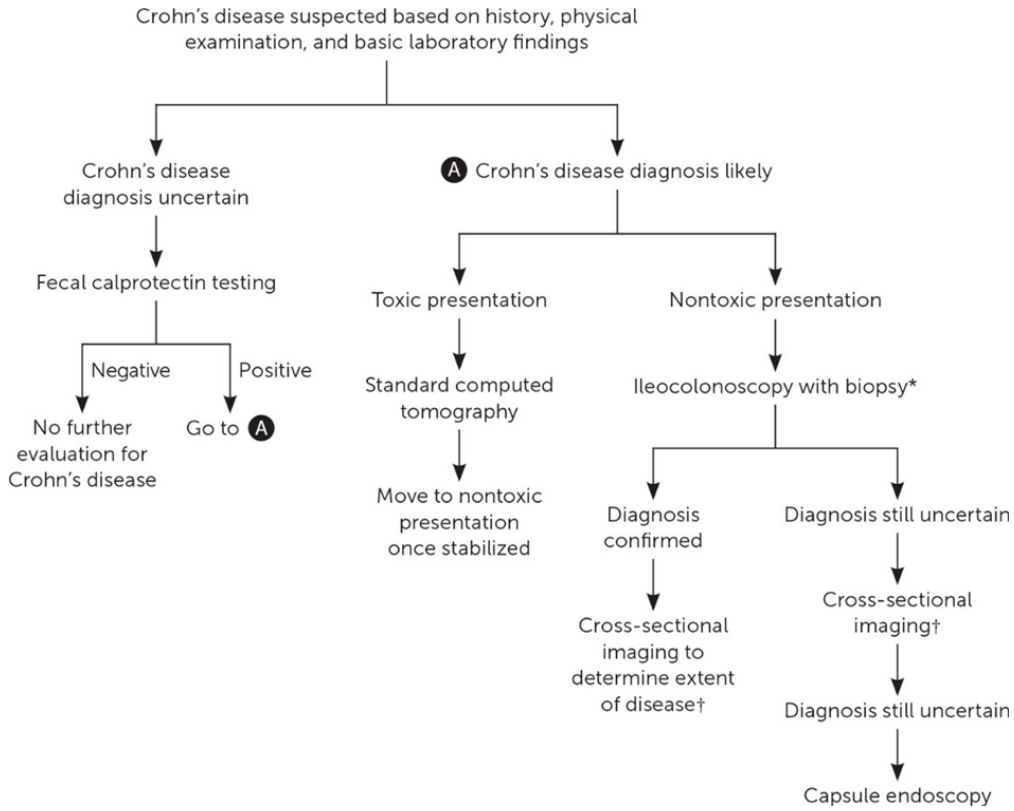

Figure 2: Demonstrates the process of a Crohn's diagnosis [8].

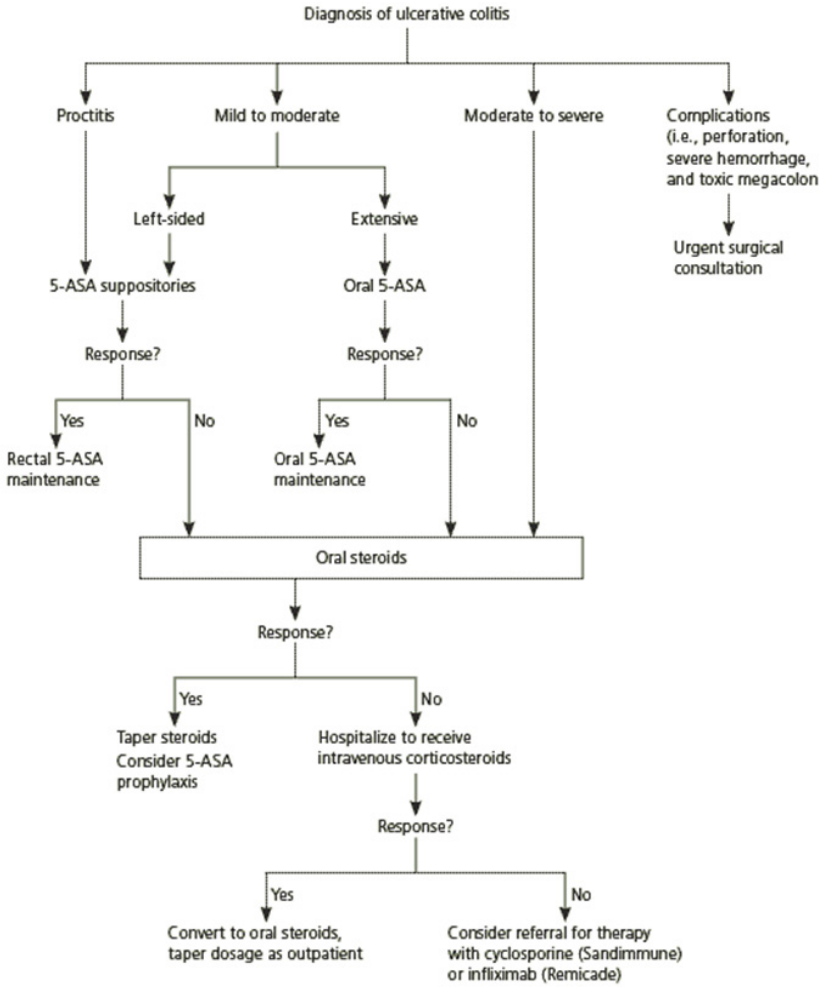

Figure 3: Demonstrates the process of an ulcerative colitis diagnosis [9].

Diagnosis of an inflammatory bowel disease requires a complete medical evaluation from a licensed physician. Endoscopic procedures are typically conducted to confirm a hypothesis created after a physician listen to patients' symptoms and family history or concluding a stool test. These endoscopic procedures include colonoscopy's, endoscopy's, sigmoidoscopy, and capsule endoscopy [2,10]. An endoscopy is a nonsurgical procedure performed by medical professionals to observe the digestive tract. Along with this, less invasive approaches such as image studies, contrast radiography, magnetic resonance imaging, and computed tomography scans are all options physicians use to diagnose inflammatory bowel disease [11].

Table 1:

Clinical Recommendations for Medical Practices	Evidence rating for Each Practice
Fecal testing	C
Cross-sectional imaging techniques (CT, MRI)	C
Eliminating smoking	B
Corticosteroids to treat flare ups	C
Biologics	C

Table Key [12]:
A = Consistent patient-oriented evidence
B = Inconsistent patient-oriented evidence
C = Disease oriented evidence

Characteristics	Crohn's	Ulcerative Colitis
Area	Any portion of GI tract	Occurs in the colon
Colonoscopy imaging	Ulcerations, gaps in lesions, cobble-stoning	Continuous inflammation within the colon
Anemia	+	++
Abdominal pain	++	+
Fistula Risk	++	+++
Colon cancer risk	++	++++

[13] + = more prevalent.

Due to the lack of an effective treatment for inflammatory bowel disease, stem cell research has increasingly become more relevant. Stem cells contain self-renewal capabilities and the capacity to produce daughter cells that undergo differentiation. One of the most important classifications of stem cells is Mesenchymal stem

cells MSCs). Mesenchymal stem cells are multipotent stem cells that are capable of differentiating. Bone marrow is typically where Mesenchymal stem cells are retrieved from, but they can also be isolated from the lungs, fetal liver, peripheral blood, cord, and fallopian tube. These cells are composed of long skinny cell bodies and enlarged nucleus. They also can self-renew by developing specialized cells while composing multipotency [14]. Autologous mesenchymal stem cells can be derived from bone marrow while allogenic mesenchymal stem cells typically require a donor. Allogenic stem cells are most idea for cell-based therapy [15].

Include more info on MSC cells and then discuss why it is important for inflammatory bowel disease.

Stem Cells

Inflammatory bowel disease is a group of pathological conditions that destruct tissue and cause inflammation in the gastrointestinal tract. Because of this, past responses to treat inflammatory bowel disease have been considerable aggressive. With recent medical advances in immunology and genetics, new treatments have been considered. Mesenchymal stem cells are described as a population of cohesive cells secluded from the bone marrow that is non-phagocytic and can differentiate into bone, cartilage, tendon, adipose, and tissue [16]. This specific stem cell works to reduce inflammation through the production of trophic factors and anti-inflammatory molecules to repair damaged tissue. These properties have inspired more than 300 clinical trials for immune-mediated inflammatory disorders. Mesenchymal stem cells were first tested to suppress in vitro T-lymphocyte proliferation. This showed the transformation into TH1 and TH17 subsets to help T cells. The stem cells were also reported to inhibit effects of cytotoxic T cells which serves as an important function in reducing inflammation [16]. The polarization of T cells to a Treg phenotype has represented models of inflammatory bowel disease. This shows that mesenchymal stem cells are not constitutively inhibitory and activate by an inflammatory environment in the host. They then mediate their immune-regulatory effects since the environment increases immunosuppressive capabilities within the cell. Mesenchymal stem cells derived from bone marrow provide the main outlet of IL-7 which plays an important developmental factor. A niche for colitogenic CD4+ is memorized T cells from bone marrow [16, 15]. Exogenous mesenchymal stem cells also have the capacity to house areas of tissue damage by secreting soluble components in microenvironments. These components stimulate the functional recovery of destroyed cells [17]. With these factors considered, stem cell therapy for inflammatory bowel disease will not only suppress inflammation but will also increase the time to retrieve remission.

Discussion

Allogeneic Mesenchymal Stem Cell therapy in Dogs with Inflammatory Bowel Disease

An individual round of mesenchymal stem cell treatment was distributed into dogs diagnosed with inflammatory bowel disease with no preexisting treatment and to another group of dogs with prednisone treatment. The two groups were observed after one, three, sex, and tweeze months to monitor albumin and cobalamin concentration. Both groups were noticed to have a decrease in disease severity due to an increase in albumin and cobalamin. Albumin is a protein and cobalamin are a nutrient in vitamin B complex. These components help repair tissue and boost bodily functions. The dogs with steroid treatment were able to gradually reduce their dosage until the treatment was eliminated. This shows the benefits of mesenchymal stem cell treatment in dot with dogs with inflammatory bowel disease no matter if they received prednisone prior. Along with this, results were documented as significant and long lasting [18].

The cells were retrieved from subcutaneous adipose tissue within falciform ligament donors through an ovariectomy. The cells were rinsed two times from a phosphate buffer saline. The cells were then incubated with 1.5% of collagenase type V at 37 degrees Celsius for half an hour. Next, the cells were washed two times with Dulbecco's Modified Eagle's medium. This medium contained 10% of fetal bovine serum that was processed through a 40-micrometer mesh of nylon. The cells were then transmitted to culture flasks with 5% carbon dioxide which expanded at 37 degrees Celsius. After forty-eight hours, non-adherent cells were eliminated. Adherent cells progressed at 80-90% confluence to trypsinization. The culture was planted at a density of 5000-6000 cells per centimeter. This medium was altered every four to seven days. After this process, the mesenchymal phenotype of the adherent cells was within regulation according to the International Society for Cellular Therapy [17].

Thirty-two dogs were observed in the study with thirteen receiving steroid treatment priors. The dogs were administered an individual dose of 4x10^6 cells/kg body weight within to the veins. Adipose derived mesenchymal stem cells were thawed and diluted with physiological saline. This altered the volume to 100 to 250 mL which was determined and established from the animal's weight. This infusion was administered within a peripheral IV cannula. The procedure averaged at half an hour of time. Each animal was monitored closely for the following hour after treatment administration. Clinical exams on hematology, serum biochemistry, albumin moderation, cobalamin moderation, serum concentration, and abdominal ultrasounds were preformed extensively. Clinical remission was eventually diagnosed with the observation of a 75% decrease of CIBDAI and CCECAI T12 values. This was because the dogs scored lower than a 3 in CIBDAI or CCECAI counts.

Allogenic Mesenchymal Stem Cell administration in human Inflammatory Bowel Disease

The first published human trial in 2006 with preliminary results for mesenchymal stem cell treatment in Crohn's consisted of 10 patients. The patients were chosen if presented with an activity index over 220 despite treatment with immunosuppressants or anti-TNF medication. Medications between a low dose of 2 million cells/kg to a high dose of 8 million cells/kg of allogenic mesenchymal cell cells derived from bone marrow were randomly asserted into patients. The treatment was collected from a third-

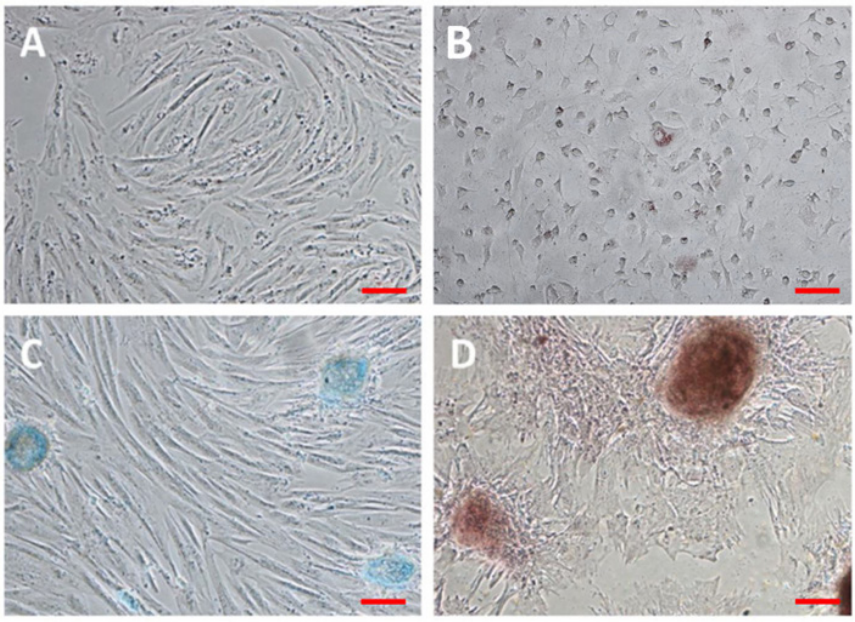

Figure 4: Compositions were altered described by the methods above and observed at 10x magnification [18].
A: Adipose derived mesenchymal stem cells; B: adipogenic; C: Chondrogenic; D: Osteogenic.

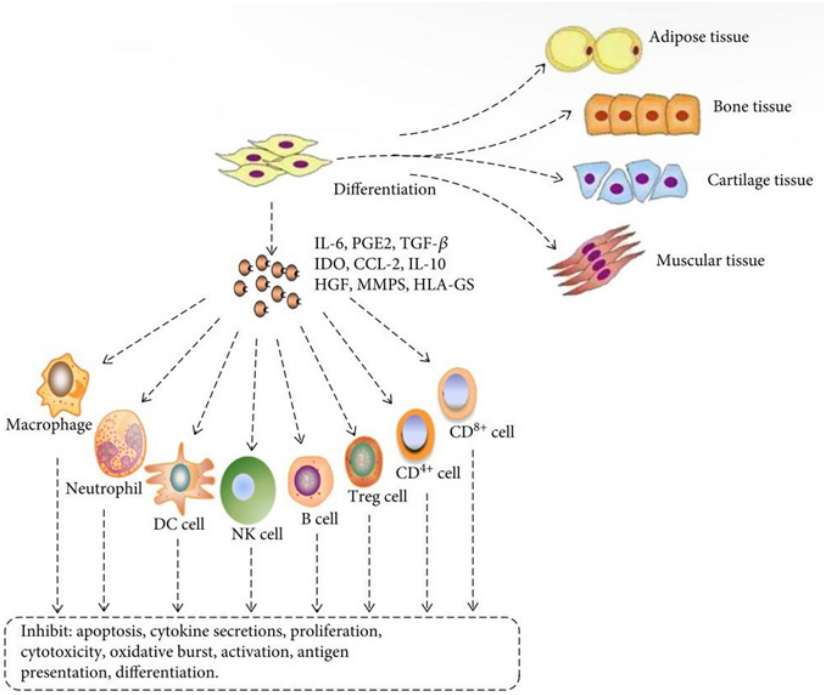

Figure 5:

party healthy donor through infusions of two doses that consisted of one week apart [16,17].

The goal for this trial was to achieve a reduction of Crohns activity to >100 in a clinical response. This decrease in activity was achieved in 3 of 9 patients within the trial. All patients in the study experienced an overall reduction some even receiving a activity score of 105 on day 28. The reduction in activity was noticed with higher dose groups. No adverse reactions were reported within the study.

Mesenchymal stem cells were observed to express CD90, CD, 73, and CD105 showing its ability to process as immunomodulatory substances. They reduce inflammation and repair damaged tissue through cytokines and growth factors. Mesenchymal stem cells within human studies were observed to adapt fast to their surroundings which enhances anti-inflammatory agents.

The general effect so mesenchymal stem cells can direct cellular differentiation of administered stem cells from adipose, bone, cartilage, and muscle tissue to replace damaged cells or it can repair

an inflamed environment through mesenchymal stem cell secretion through cytokines influenced through an immune system [19].

Mesenchymal Stem Cell Therapy to treat Ulcerative Colitis in Humans

Ulcerative colitis is a chronic condition resulting in idiopathic inflammation within the large intestine [20]. A study started in 2020 to observe the efficiency of mesenchymal stem cells within ulcerative colitis.

The study consists of 24 humans diagnosed with ulcerative colitis, an inflammatory bowel disease. Patients will be infused with allogenic bone marrow mesenchymal stem cells with a dose of 150 to 300 million per dose randomly assigned to a group of participants within the study. Patients were then observed at 3 months after the injection. Many participants achieved clinical remission while others delayed the need for surgery. Patients will be examined thoroughly for two years post treatment. The results of this trial will be completed in November 2023. The goal of the end of the trial will be for the endoscopic injection of remestemcel-L expanded by allogenic mesenchymal stem cells served from bone marrow to effectively treat ulcerative colitis [21].

Mesenchymal Stem Cell Therapy to treat Inflammatory Bowel Disease with Fistula

Inflammatory bowel disease has a high risk of fistulas with anorectal fistulas being the most common. Anorectal fistulas are typically treated through fistulotomy which is a surgical procedure. Patients diagnosed with inflammatory bowel disease and fistulas often experience excessive pain. Mesenchymal stem cells were researched for reconstruction of healthy crissum tissue. Along with this, the specific stem cell-based therapy was researched further to decrease pain and improve the quality of life for individuals with inflammatory bowel disease and fistulas [22].

The U.S. Food and Drug Administration (FDA) approved of Prochymal therapy in 2009 to treat patients with inflammatory bowel disease and fistulas [23]. The mesenchymal stem cells in this treatment were retrieved from bone marrow. Along with this product, the Ministry of Food and Drug Safety of Korea approved the medication Cupistem in 2012. This mesenchymal stem cells were derived from autologous adipose [24]. This consisted of the administration of 3 x 10^7 per cell/mL mesenchymal stem cells derived from adipose tissue. This treatment promoted tissue repair and reduced reoccurrence of fistula in patients [22].

Mesenchymal stem cells contain immunomodulatory properties. These essential properties are associated with the release of cytokines, chemokines, and growth factors [22]. Along with this, the immunomodulatory properties of mesenchymal stem cells have been shows to suppress T cell proliferation, suppress B cell proliferation and terminal differentiation, influence dendritic cell maturation and function, and immune modulation of immune cells [22,25]. This is important for healing damaged tissue cells.

Mesenchymal stem cells are commonly derived from bone marrow which can be utilized for autologous or allogenic transplantation. A study done by Dijvestein et. al., administered mesenchymal stem cells derived from bone marrow twice a day for a full week to nine clinically diagnosed patients with inflammatory bowel disease. These infusions were composed of 1-2x10^6 bone marrow derived mesenchymal stem cells per kilogram of body weight. Six out of nine patients experienced a decrease in inflammation activity of > 70%. The remaining three patients in the study required surgery to relieve symptoms. This study experienced no serious side effects during or after infusions [22,26].

A study conducted by Ciccocioppo et. al., researched treatment options for ten patients diagnosed with inflammatory bowel disease and fistulas. Patients were administered monthly injections of 2x10^7 bone marrow derived mesenchymal stem cells expanded by ex vivo. These patients were observed through magnetic resonance imaging (MRI). Within 12 months, an endoscopic procedure was conducted to observe the full effect of the medication. After this observation, 70% of patients achieved complete fistula closure while 30% retained incomplete fistula tracks but experienced reduction in inflammation. Rectal mucosal was improved after treatment concluded and no adverse side effects were observed [22,27].

Local administration of mesenchymal stem cells typically bone marrow derived have been shown to improve fistulas within individuals pertaining an inflammatory bowel disease. This can reduce the need for invasive treatments such as surgery. Clinical trials researching treatment plans overall experienced a positive clinical response due to anti-inflammatory and anti-fibrotic properties [22,28].

Conclusion

Due to their widely observed immunomodulatory properties that can reduce inflammation and repair damaged tissue, mesenchymal stem cells are a promising treatment for inflammatory bowel disease. Clinical trials conducted on dogs and humans have demonstrated the safety and effectiveness of mesenchymal stem cell treatments. Treatment for inflammatory bowel disease has consistently improved for the past 20 years. Mesenchymal stem cells will continue to provide promising results for patients with inflammatory bowel disease.

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