Injection of Autologous Mesenchymal Cells for the Treatment of Arthritis has so far been Found to be Completely Safe

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Abstract

Background: Injection of autologous mesenchymal stem cells (AMSCs) as stromal vascular fraction, culture expanded adipose derived stem cells, minimally manipulated fat graft, bone marrow aspirate or cultured bone marrow MSCs, for osteo- and inflammatory arthritis have shown good clinical efficacy in many studies. Questions have been raised as to their safety despite no evidence known to us that they are unsafe when used this way. We hypothesized that AMSC injections are completely safe for the treatment of arthritis. **Methods:** A PubMed literature search was performed to identify adverse events specifically related to the injection of autologous mesenchymal or hematopoietic stem cells into arthritic joints or intravenously. **Results:** 2,011 reported injections were found. No stem cell specific adverse events were identified. Specifically no infections, tumorigenesis, or chondrolysis from collagenase were found. **Conclusions:** Intra-articular injection of autologous mesenchymal stem cells for the treatment of arthritis is completely safe with no stem cell specific adverse events yet documented, and no increased risk compared with other traditional treatments for arthritis.

Keywords: mesenchymal stem cell; stromal vascular fraction; arthritis; osteoarthritis; adverse event

1. Introduction

The injection of autologous mesenchymal stem cells (AMSCs) for the treatment of osteo- and inflammatory arthritis has shown good clinical efficacy in many studies when injected intra-articularly (IA) or intra-venously (IV), often allowing avoidance of surgery **[1-5]**. AMSCs are

used in several forms including stromal vascular fraction (SVF), culture expanded adipose derived stem cells, minimally manipulated fat graft, bone marrow aspirate or cultured expanded bone marrow. Some have questioned whether AMSC injections are safe, despite the lack of any evidence of risk known to us when used for arthritis.

Stem-cell-treatment-specific adverse events can be divided into those potentially resulting from stem cell joint injection: namely increased infection risk, tumorigenesis, collagenase induced chondrolysis, or accelerated disease progression; and those potentially resulting from intra-venous injection for those protocols where IV injection is done: namely stroke, fat embolism, pulmonary embolism, or cardiac event. Our goal was to find out whether these potential adverse events have ever been found to actually occur.

Stem cell treatments involve several standard medical procedures which are generally safe but, as with all procedures, have occasional adverse events. These procedures, with referenced adverse events are Lipoaspiration **[6]**, bone marrow aspiration **[7, 8]**, intra-articular injection **[9, 10]**, intra-venous injection **[11]**, and storing tissue in a tissue bank **[12-15]**. These potential adverse events can occur whether or not stem cells are used and are not inherent to stem cell treatment, and are not the focus of this paper.

Minor side effects that can occur with the injection of a joint with any injectate, such as acute self-limited non-infectious local pain and swelling at the injection site are not the focus of this study; since these are also not risks related to stem cell treatment. Incidental tumors in an incidence that would normally occur and at a site remote from the injection are also not the focus of this study since there is no reason to think they were related to the stem cell treatment.
The US FDA specifically prohibits, and the European Union EMA recommends against, the treatment of fat with collagenase to make “stromal vascular fraction,” or the culture expansion of

MSCs: arguing that the tissue or cells are being thereby more than minimally manipulated – which they prohibit as resulting in risk to patients. It has been our impression based on the scientific literature and our clinical experience that such intra-articular or intravenous injections are completely safe when used as treatment for osteo or inflammatory arthritis. Furthermore the body uses stem cells to repair tissue mitigate inflammation. Thus AMSC injection is really only assisting a natural process without introducing any unnatural substances. This would be expected to be safe. We hypothesized that a PubMed literature review would show AMSC injections for arthritis to be completely safe.

2. Materials and Methods

We performed a comprehensive literature search for the treatment of osteoarthritis and inflammatory arthritis with AMSCs. Using the PubMed search engine, we searched the following terms in various combination to find articles published in national library of medicine peer reviewed journals that had carried out clinical trials with MSCs in humans: “osteoarthritis/arthrosis”, “rheumatoid arthritis”, “stem cell”, “mesenchymal stem cell”, “MSC”, “stromal vascular fraction”, “SVF”, “minimally manipulated fat”, “micro-fragmented fat”, “adipose-derived stem cell”, “bone marrow derived stem cell”, “cultured stem cell”, and “bone marrow aspirate”. In addition, we reviewed the references of the articles found this way to find other articles potentially matching our criteria. Figure 1 demonstrates our study selection process. We excluded articles in which stem c ells were used in conjunction with immunosuppression or surgery. Hematopoietic and allogeneic stem cells were excluded. Only articles published on PubMed were included. We only studied MSCs used by themselves, and

only autologous tissue, because we believe this is the highest and best use of this tissue: no medications, no surgery, no immunosuppression, no subtle allogeneic rejection phenomena potentially compromising efficacy. We also limited our study to autologous MSCs used by themselves because of the tremendous safety profile when they are used this way and because autologous tissue is generally safer than allogeneic.

Any major stem cell specific adverse event as defined in the introduction was noted. Side effects resulting from standard medical procedures, minor side effects resulting from any joint injections, and remote incidental tumors were excluded from comment, as this paper focuses on major stem cell specific adverse events as elucidated in the introduction.

3. Results

Forty-one studies were found that fit our search criteria (see Table 1). Eight of the papers used fat treated with collagenase to produce stromal vascular fraction, 20 of the papers used cultured fat or bone marrow; and 13 papers used "minimally manipulated" fat and/or bone marrow. Forty of the studies used intraarticular injections while one study used intravenous injections. Follow up time ranged from 3 months to 60 months, with an average follow up time of 16 months. In total, 2,011 treatments were performed on 1,826 patients in the studies we identified.

We found a zero incidence of stem cell related adverse events after intraarticular injection. Only one study used autologous mesenchymal stem cells intravenously, and also did not have any stem cell related adverse events

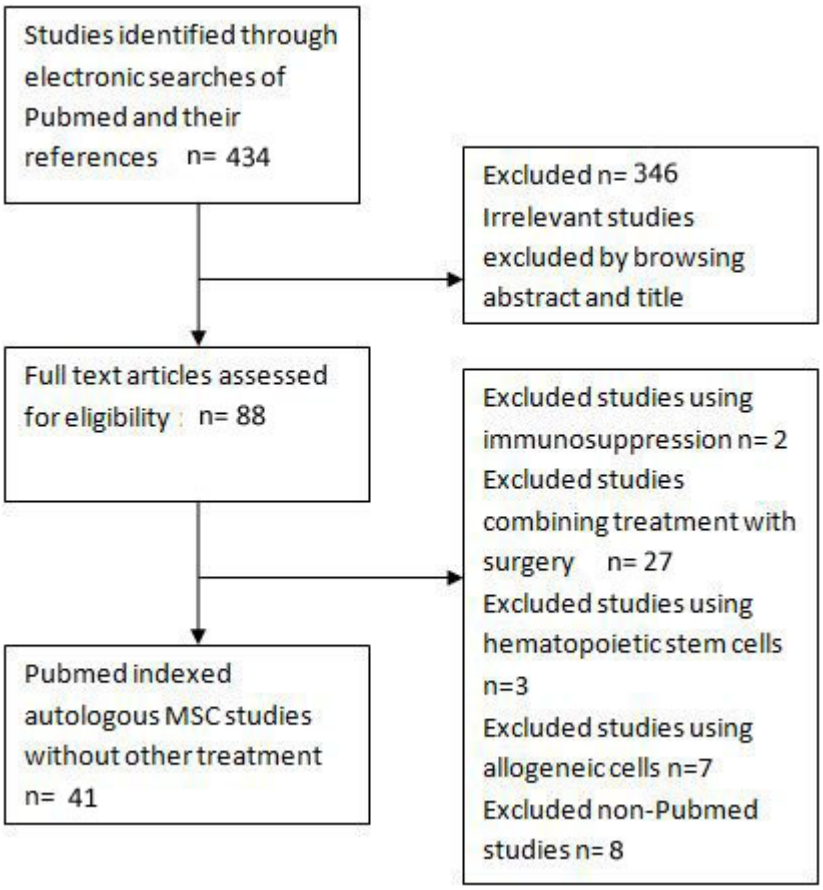

Figure 1. Study selection of peer reviewed autologous mesenchymal stem cells treatments for arthritis.

Table 1. Summary table of MSC studies treating Arthritis.

Author/Year	Cell type	Route	Number of Treatments	Number of Patients Receiving Treatment	Type of Arthritis Treated	Follow-Up duration (months)	Major Reported Stem-Cell Related Adverse Events
Al-najar-2017 [16]	cultured BMD-MSC	IA	13	13	OA	24	None
Anz 2020 [17]	BMAC	IA	45	45	OA	12	None
Bansal-2017 [3]	SVF	IA	10	10	OA	24	None
Bastos-2018 [4]	cultured BMD-MSC	IA	18	18	OA	12	None
Centeno-2015 [18]	BMAC	IA	424	358	OA	12	None

Centeno-2014 [19]	BMAC + adipose graft	IA	224	224	OA	6	None
Centeno-2011 [20]	Cultured BMD-MSC	IA	339	339	OA	12	None
Dall'Oca-2019 [21]	minimally manipulated fat	IA	6	6	OA	6	None
Davatchi-2016 [22]	cultured BMD-MSC	IA	4	3	OA	60	None
Emadedin-2012 [23]	cultured BMD-MSC	IA	6	6	OA	12	None
Emadedin-2015 [24]	cultured BMD-MSC	IA	15	15	OA	30	None
Emadedin-2018 [25]	cultured BMD-MSC	IA	19	19	OA	6	None
Fodor-2016 [1]	SVF	IA	6	6	OA	12	None
Freitag-2019 [2]	cultured AD-MSC	IA	20	20	OA	12	None
Garay-Mendoza-2018 [26]	BMAC	IA	30	30	OA	6	None
Garza-2015 [27]	SVF	IA	6	6	OA	3	None
Ghoryani-2019 [28]	cultured BMD-MSC	IV	9	9	RA	12	None
Gibbs-2015 [29]	SVF	IA	7	4	OA	12	None
Hong 2019 [30]	SVF	IA	16	16	OA	12	None
Hudetz-2017 [31]	microfragmented fat	IA	17	17	OA	24	None
Jo-2017 [32]	cultured AD-MSC	IA	18	18	OA	24	None
Kim-2014 [33]	BMAC & minimally manipulated fat	IA	75	41	OA	12	None
Lamo-espinosa-2018 [34, 35]	cultured BMD-MSC	IA	20	20	OA	48	None
Lee-2019 [36]	cultured AD-MSC	IA	12	12	OA	6	None
Lu -2019 [37]	cultured AD-MSC	IA	26	26	OA	12	None
Mardones-2017 [38]	cultured BMD-MSC	IA	10	10	OA	16-40	None
Mautner 2018 [39]	BMAC	IA	58	41	OA	6	None
Mautner 2018 [39]	Minimally	IA	48	35	OA	6	None

	manipulated fat						
Orozco-2014 [40, 41]	cultured BMD-MSC	IA	12	12	OA	24	None
Pak-2013 [42]	SVF	IA	100	91	OA	26	None
Pers-2016 [43]	cultured AD-MSC	IA	18	18	OA	6	None
Pintat-2017 [44]	SVF	IA	19	19	OA	12	None
Roato-2018 [45]	minimally manipulated fat	IA	20	20	OA	18	None
Rodriguez-Fontan 2018 [46]	BMAC	IA	10	10	OA	24	None
Sampson 2016 [47]	BMAC	IA	100	73	OA	2-22	None
Shadmanfar-2018 [48]	cultured BMD-MSC	IA	15	15	RA	12	None
Shapiro-2016 [49]	BMAC	IA	25	25	OA	6	None
Soler-2016 [50]	cultured BMD-MSC	IA	15	15	OA	12	None
Song-2018 [51]	cultured AD-MSC	IA	18	18	OA	24	None
Spasovski 2017 [52]	Cultured AD-MSC	IA	11	9	OA	18	None
Themisocleous 2018 [53]	BMAC	IA	121	121	OA	6-30	None
Yokota-2017 [5]	SVF	IA	26	13	OA	6	None

BMD-MSC: bone marrow derived mesenchymal stem cells

AD-MSC: Adipose derived mesenchymal stem cells

SVF: stromal vascular fraction

BMAC: bone marrow aspirate concentrate

IA: intraarticular

IV: intravenous

OA: osteoarthritis

RA: rheumatoid arthritis

4. Discussion

This paper is the first to our knowledge to specifically address the safety of autologous non-embryonic mesenchymal cells for the treatment of arthritis.

Potential Stem Cell Specific Risks of Treatment:

Although no significant risk or stem cell specific adverse events were found, it is important to discuss why this result is expected. The four potential risks that could have been related to stem cell treatment are: 1) Chondrolysis [54, 55] from collagenase injury[56], 2) Tumorigenesis from injected tissue[57], 3) Infection, and 4) IV injection related adverse events. These will be considered in turn. All were considered unlikely to occur, but first we will discuss stem cell treatment types that were excluded from this study.

Excluded Studies Using MSCs and Surgery or Immunosuppression

Some have administered autologous MSCs previously obtained from apheresis after a course of immunosuppression [58, 59]. Still others have combined stem cells with surgery [60-64]. In all these cases morbidity or mortality can occur as a result of these associated treatments, not from the AMSCs. Our study specifically focused on AMSCs used without these other modes of treatment to identify any potential problems used with MSCs alone. We also did this because we believe the highest and best use of MSCs occurs without these other treatments. So our choice highlights the safety of the very treatments with the most useful clinical applications.

Exclusion of Studies Using Allogeneic Tissue

We also specifically excluded studies using allogeneic tissue [65-70]. Allogeneic tissue carries a potential risk of rejection [71] and a greater risk of problems related to processing [72].

It has also been shown to be generally less effective than autologous tissue. For all these reasons this study focused only on autologous tissue.

Collagenase Induced Chondrolysis:

While high dose collagenase has been used in animal studies to model inflammatory arthritis [73], chondrolysis after human stem cell treatment where collagenase is used has never been reported. It should be noted that collagenase is destructive only in high doses applied directly to the joint. Most human treatment protocols and devices for the enzymatic digestion of fat to produce SVF involve washing the collagenase from the stem cells after enzymatic digestion [74]. However, even in the cases where collagenase is merely suctioned off after digestion [75], no adverse events have been seen. This demonstrates that the use of collagenase to produce SVF is a benign treatment, thus it is not surprising that the risk from collagenase treated fat has been zero.

Tumorigenesis:

Bone marrow and concentrated bone marrow have been used for decades for orthopaedic applications, such as treatment for non-union fractures [76]. More recently, cultured bone marrow cells have been used for the treatment of arthritis [4, 16, 20, 22-25, 28, 34, 35, 38, 40, 41, 48, 50]. Microfracture and Pridie drilling rely on the introduction of stem and other bone marrow cells into the surface of a joint from the bone marrow to grow fibrocartilage and have been performed for more than forty years [77]. In these procedures, while new fibrocartilage tissue is created within a joint, no tumorigenesis has even been reported. This is analogous to

bone marrow stem cell injection procedures into arthritic joints. There are no reports of tumorigenesis in any of these applications.

Similarly, fat from one part of the body has been injected into other areas of the body for decades in plastic surgical applications [78], and along inflamed nerves after lumbar laminectomy [79]. There are no reports of tumorigenesis when fat alone is used.

Infection:

There have been no infections reported in the PubMed literature after injection of AMSCs in a joint and/or intravenously. Since AMSCs have reported anti-bacterial properties, this is not surprising [80].

Intra-Venous Injection:

Intra-venous injection should be rendered completely safe by filtration with a standard blood filter as is used with blood transfusion. No embolic, thrombotic or other adverse event has ever been reported from such usage with MSCs. Again this complete safety is to be expected.

Weaknesses:

A potential weakness of this study is that there could be adverse events that are not reported. However, the 1,605 safe treatments in this review event make it extremely unlikely that a significant number of adverse events exist outside these studies. As discussed below, even this weakness is mitigated by the complete absence of infection risk in the many animal studies injecting MSCs [81-86].

Strengths:

A strength of this study is the large number of patients treated without adverse event. Additionally, even in animal studies, we are not aware of reported stem cell specific adverse events [87]. There is thus every reason to expect that the extraordinary safety reported here is valid.

Other work from our center has shown that AMSC treatment is effective for the treatment of arthritis [88]. The results of this study validate that it is also completely safe, with the best safety profile of any of the common non-surgical treatments of arthritis: namely non-steroidal anti-inflammatory drugs, other medications, and steroid injections.

The use of AMSCs is restricted throughout the United States, Europe, and elsewhere based on concerns of safety and efficacy. This study shows that AMSC use should not be restricted based on concerns for safety. The unwarranted restriction of AMSC use based on unfounded fears of lack of safety and efficacy results in tremendous and avoidable morbidity, mortality and cost. The wide application of autologous AMSCs for the treatment of arthritis would result in decreased morbidity and mortality by allowing substantial reduction in the use NSAIDs, opiates and corticosteroids. NSAIDs alone have been estimated to cause over 16,500 deaths in the United States annually [89] and the treatment of joint pain is the largest indication for their use [90]. In fact the “conservative,” that is non-operative, treatment of arthritis with these drugs has been estimated to result in even higher morbidity and mortality than joint replacement surgery [91]. Similarly, opiod use for treatment of arthritis has resulted in addiction and overdose issues, increased risks of falls with resulting fractures, and overall increased mortality without providing good relief of symptoms. [92-95]

Increased use of MSCs for arthrosis would also result in a substantial decrease in the rate of total joint replacement surgery. Joint replacement surgery has been associated with a one year mortality of 1%, translating to 15,000 annual deaths for the 1.5 million knee and hip replacements performed in the United States [96, 97]. An additional 22,000 joints replacements result in infection [98]. The five year mortality of infected joint replacement is roughly 35% [99], translating to an additional 7,000 annual deaths from joint replacement. This does not include the morbidity of chronic antibiotic use, and repeated surgeries, including amputation. The economic cost of treating the complications from NSAID use and from failed and infected joint replacement is also staggering and beyond the scope of this paper, but is clearly in the billions of dollars annually in the US alone. The cost of a single infected joint replacement has been shown to exceed $50,000 [100] for an annual national cost of at least 1 billion dollars. Deaths from NSAIDs and joint replacement surgery carry a monetary cost of the associated medical care, and an emotional cost that is incalculable. Widespread use of MSC treatment would result in greatly reduced suffering and would save thousands of lives.

Thus this over-protection of the populace by well-meaning, concerned, and compassionate regulatory bodies that restrict MSC use carries an unintended but enormous cost in suffering, death, and health care dollars spent. The multi-faceted real costs of over-regulation are only now beginning to be explored [101]. It should also be realized that autologous MSC treatment uses only a patient's own tissue. No regulatory body has jurisdiction in this area, absent a clear and overriding safety concern. And as we have shown, no such concern for safety or efficacy exists for MSCs.

4. Conclusion

Intra-articular injection of autologous MSCs, including cultured and collagenase-treated tissue, for arthritis is completely safe. The use of these treatments should not be restricted based on safety concerns.

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