The debit side of stem cell joint injections: a prospective cohort study

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ABSTRACT

Background:
There is little long-term information and no prior report that used independently collected data describing the effectiveness and complications of intraarticular injections of stem cells.

Methods:
This study reviewed the records of 2964 patients who received stem-cell injections in the hip, knee, or shoulder and 2971 patients who had injections of steroids or viscosupplementation (comparison group).

Results:
Pain improved initially in 2104 (71%) of patients. At a mean follow-up of 5.6 yr, 563 (15%) patients continued to report less pain and the mean time of pain reduction was 17 mo (range, 1 to 84 mo). The mean cost of stem-cell care was $6000 (range, $1200 to $13,000). There were 115 (8%) complications using autologous stem cells, 113 (8%) with donor cells, and 13 (9%) when both were used. Stem-cell complications included six tumors, 14 infections, 48 syncopal, arrhythmia, seizure, or vasovagal reactions, 42 chronic culture-negative effusions, 18 injection site rashes, 44 instances of systemic viral like syndrome or herpes zoster-like reactions, 31 new allergies, and 39 instances of acute and severe worsening of pain and function. There were 82 hospitalizations. For the comparison group, there were 61 (2%) complications and eight hospitalizations.

Conclusions:
The frequency (8%) and severity of complications with stem cell-injections is higher than for steroid or viscosupplementation injections (2%). Stem-cell joint injections are a costly and speculative treatment and should only be used with a deep understanding of the risk. Practitioners providing stem cell joint injections must include long-term follow-up as part of their care. Additional validated scientific studies are needed.

Level of Evidence:
Level II.

Key Words
stem cells, intraarticular injections, complications

INTRODUCTION

Stem-cell infusions were first reported in 1951 for treatment of bone marrow aplasia resulting from accidental radiation exposure and aplastic anemia after chemotherapy.[1] The stem cells were obtained from volunteer donors, cadavers, or feti. Stem-cell infusions were unsuccessful at first because of rejection, except for a few patients whose identical twins were donors.[2–4] In 1970, E. Donnall Thomas, MD reported the first successful bone marrow rescue using a bone marrow allograft. The patient had leukemia and had been treated with whole body irradiation.[5] The Thomas laboratory was then at Seattle's Providence Hospital. Drs. Sauvage and Dedomenico performed their initial experiments with coronary artery bypass grafting in dogs in an adjacent laboratory.[6] The Thomas and Sauvage laboratories sometimes shared dogs.[6] Marrow-derived stem cells were infused both intravenously and, occasionally, intraarticularly in both dogs and patients for joint pain that was experienced during their experimental treatments.[3,4,7,8] The joint symptoms usually improved.[2] Dr. Thomas won the Nobel Prize in 1990 for his stem-cell research.[9]

There are many published reports of remarkably good results from injecting stem cells into joints, tendons, and other tissues.[10–16] The superiority of stem-cell injections over other treatments in providing freedom from pain and restoring range of motion and function has been reported in many journals. Regeneration of cartilage and tendons has been claimed but not proven.[11,15–18] There are no completed clinical trials translating cellular therapies from Phase I/IIa first-in-man studies through Phase III documenting regeneration of articular cartilage. Complications can be difficult to identify because they may take years to develop. Some complications are not immediately apparent to the patient or are not reported or understood by the treating practitioner. Despite the absence of compelling evidence from clinical trials, some physicians assert that stem cells have a unique capacity to restore tissue health because they can sense their environment and differentiate in a manner that repairs the tissue defect. It is also argued that conducting controlled trials is too complex except for industrial sponsors and that waiting for results of studies denies patients the benefits they need now. Advocates claim that broad use of stem cells in clinical practice should be allowed and encouraged until evidence regarding efficacy is gathered. The stem-cell therapies

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in current use have been described as unproven.[19] Proponents generally assert that stem-cell therapies are quite safe, particularly when the cells are autologous.[11,15,18,20,21] The demand for stem-cell therapies in orthopaedics is driven by the limited effectiveness of treatments for osteoarthritis. Patients are interested in a treatment that does not involve joint replacement.

The questions asked in this study are: What are the nature and frequency of complications from stem-cell injections? Are stem-cell complications recognized by the same practitioners that provide the injections? Are stem-cell injection complications serious, and do they require additional treatment? Do stem-cell injections reduce pain and for what duration? The hypothesis of this study was that the safety and efficacy of stem-cell injections may not match the claims and expectations of patients and their treating physicians.

METHODS

Ethical Review and Study Design

Because all data were deidentified, the study was exempt from institutional review board approval. The health plan collected the medical information and provided an informed consent and privacy document for patients who were enrolled in this prospective study. All information was deidentified, and this research involved neither protected health information nor an identifiable human subject. For the purposes of this report, stem cells from both patients and donated sources were included and combined. The cells were concentrated but only minimal manipulation was performed that was consistent with United States Food and Drug Administration (FDA) exemptions and ethical guidelines. None of the patients included in this report were enrolled in registered clinical trials. All patients were treated at their own time, trouble, and expense by practitioners in community practice. All patients provided records of their treatment method and its cost.

Patient Selection

This study reviewed the records of 9,088 patients in an insurance company database who received stem-cell, steroid, or viscosupplementation injections in their hip, knee, or shoulder between 2012 and 2015. The inclusion criteria were all patients with osteoarthritis receiving autologous or allogeneic stem-cell injections into their hip, knee, or shoulder. All patients were adults with complete medical records who had a minimum of 4 yr follow-up. The indications for injection were pain that was unrelieved by activity modification, nonsteroidal medications, and physical therapy.

Of the 9,088 patients who were originally in the database, 6,117 patients received intraarticular stem-cell injections. Of the patients who received stem cells, 429 (7%) were lost to follow-up, and 134 (2%) died before the 4-year minimum follow-up period and were excluded from additional analysis. Another 2591 patients had other treatments such as surgery or other injections into their joint before the minimum 4-year follow-up and were excluded from the study to increase the confidence that the complication was related to the stem-cell therapy and not to a subsequent treatment. The remaining 2964 patients comprised the stem-cell study population. The stem-cell injection group was compared to a group of 2971 patients who received steroid or viscosupplementation injections.

Data Collection

The database was provided by a consulting group within an insurer. This consulting firm provided advice and administrative service in support of employee benefit programs administering Health Savings Accounts (HSA) and Flexible Savings Accounts (FSA). Payment for stem-cell injections is not a covered service under most health insurance plans because the treatment is considered experimental or investigational by most insurers. However, with medical necessity documentation and proof of medical treatment, payment is possible for stem-cell injection under many HSA and FSA programs. The consulting firm also provided consulting for the health benefit programs associated with the HSA and FSA accounts and had access to the medical records documenting the complications that occurred.

All injections were provided in the office, and none were performed in the operating room or lab. Sterile skin preparation and technique with gloves was used for each injection. The exact preparations that were injected varied. Four years was selected to capture late complications.

Steroids or viscosupplementation were injected into 624 (21%) hips, 1782 (60%) knees, or 565 (19%) shoulders and were followed for a mean of 5.1 yr (range 4 to 6.5 yr). The stem-cell injections were in 622 (21%) hips, in 1808 (61%) knees, and in 534 (18%) shoulders, with a mean follow-up of 5.6 yr (range 4 to 7 yr).

Complications that were assessed were tumor formation, infection, chronic culture-negative effusion, rash or injection-site reactions, recurrent bloody or clear effusion, substantial worsening of pain (requiring additional treatment or use of a walking aid), adverse reaction to injection (e.g., vasovagal, syncope, arrhythmia) requiring treatment, herpes zoster or viral-like syndrome after injection, and development of new allergies. Other symptoms that were reported such as injection site pain without other reaction, headaches, depression, and malaise were not included. The adverse reactions that were reported were compared to the pretreatment extensive systems review that was available within the patient's health record. If the conditions after injection were not new by comparison to the systems review information, or there were other explanations for the symptoms, they were not included as complications. Patients were asked if their pain improved after their stem-cell treatment and for how long it was improved. Improvement meant that the pain improved by 2 or more points on the 10-point analog pain scale. This question was asked at year 4 and annually thereafter. The analysts recording the information about complications and results were blinded as to whether stem cells or other treatments had been provided.

Statistical Analysis

The sample size was calculated for a statistical power of 0.9 (90%). The sample size in each group needed to achieve an

TABLE 1. Patient demographics

Variable	Stem cells	Steroids or viscosupplementation
Patients (n)	2964	2971
Gender		
Male	1513	1502
Female	1424	1443
Nonbinary	27	28
Injections (n)		
Knee	1748	1782
Hip	711	624
Shoulder	505	565
Mean follow-up (range)	5.6 (4 to 7) years	5.1 (4 to 6.5) years
Mean cost (range)	$6,000 ($1200 to $13,000)	$440 ($120 to $780)

error rate of 0.0001 was 2622. The software used was SPSS, version 16.0 (IBM, New York, NY). Statistical analyses of complications were provided using SPSS version 16.0. Statistical significance was set at $P<0.05$. The chi-square statistic was used. Any missing data elements were excluded from analysis with no imputation performed.

RESULTS

Patient demographics for study and comparison groups are shown in Table 1. There were 2104 (71%) patients who reported initial improvement in their pain and 563 (15%) patients who continued to report reduced pain at a mean of 5.6 yr. The mean duration of improvement was 17 mo (range 1 to 84 mo). There were 301 (10%) patients who had two injections and 28 (1%) patients who had three injections; no patient had more than three injections. There were 1423 (48%) patients who received autologous cells, 1393 (47%) who received donor cells, and 148 (5%) patients who received both.

There were no deaths attributed to stem-cell injections. One patient died the evening after the injection, and another died the next day but in each instance the death certificate did not list the stem-cell injection as a contributing cause. No autopsy was performed for either patient, so an exact cause of death was not known.

There were 82 patients (2.9%) who were hospitalized for the following reasons: infection (14), rule out infection (16), tumor (six), adverse reaction (e.g., arrhythmia, syncope, seizure, vasovagal) (22), systemic allergic reaction (seven), local allergic reaction (three), pain or dysfunction (five), viral-like syndrome or herpes zoster (nine). The practitioner who provided the injection was the admitting or consulting physician for 39 (46%) of the 82 admitted patients.

The complications are shown in Table 2. Complications occurred in 241 (8.2%) patients with stem-cell injections. The complication was diagnosed by the practitioner who provided the injection in 109 (45%) of patients and by another practitioner in 132 (55%) patients. There were 115 (8%) complications with autologous stem cells, 113 (8%) with donor cells, and 13 (9%) when both were used. Complications occurred in 61 (2%) patients with viscosupplementation or steroid injections. There were eight hospital admissions for patients with viscosupplementation or steroid injections. Complications after stem-cell injections occurred in 147 (61% of complications) knees, 51 (21%) hips, and 43 (18%) shoulders. Complications occurred in 37 knees (61% of complications), 12 (20%) hips, and 12 (19%) shoulder in the comparison group.

Clear or bloody effusion was not significantly different between the groups. The rate of infection, syncope, vasovagal reaction, arrhythmia, septicemia, and injection site reaction or rash was significantly higher ($P<0.05$) in the stem-cell group. The rate of worsening pain or function, chronic effusion, viral syndrome, and development of new allergies was higher at the highly significant level of ($P<0.0001$). Tumor formation was statistically higher in the stem-cell injection group at the $P<0.001$ level.

In the stem-cell group, all six tumors (two shoulder, two hip, and two knee) were benign, and four were excised successfully with no recurrence. Three tumors were in patients with autologous cells, and three were in patients with allogeneic cells. One patient refused tumor excision from his shoulder and was being followed. One tumor in the knee recurred and was excised a second time. Ultrasound and fluoroscopy were used on all hips, ultrasound was used in 64% of knees. In the remainder of the knees, the intra-articular placement of the needle was confirmed by joint fluid return. Ultrasound was used in 32% of shoulders, fluoroscopy in 33% of shoulders, and fluid return in 35%. No evidence of metastasis was found in any patient. Pathological analysis varied but showed densely cellular, highly proliferative primitive cells with primarily fibrous differentiation in each patient. DNA fingerprinting analysis was performed in

TABLE 2. Complications

Complication	Stem cells (n = 2964)	Steroid or viscosupplementation (n = 2971)	P
Tumor	6 (0.2)	0 (0)	< 0.001
Infection	14 (0.5)	2 (0.6)	= 0.0013
Chronic effusion	42 (1.4)	12 (0.4)	< 0.0001
Vasovagal, syncope, arrhythmia, septicemia	41 (1.4)	21 (0.07)	= 0.0082
Worsening pain and function	39 (1.3)	10 (0.3)	< 0.0001
Rash, injection site reaction	18 (0.6)	2 (0.06)	= 0.003
Clear or bloody effusion	17 (0.6)	12 (0.4)	= 0.27
Herpes zoster, viral syndrome	34 (1.1)	1 (0.03)	< 0.0001
Development of new allergies	31 (1.0)	1 (0.03)	< 0.0001
Total	241 (8.2)	61 (2.0)	< 0.0001

three patients and showed that the tumors were predominantly composed of nonhost cells. Based on histopathological and molecular studies, these tumors were from the intraarticularly introduced stem cells. The tumors did not show features typical of malignancy; no cancer-linked genetic aberrations were detected on next-generation sequencing in three tumors. The tumors that were found were neoplasms (i.e., a "new growth"), but they were not well assigned to any type of previously characterized neoplasms based on the pathology.

All 14 infections in the stem-cell group were culture proven and required treatment: 11 (80%) were Staphylococcus infections (aureus, epidermidis, and lugdenensis). Two patients were treated for septicemia, 10 patients with a joint infection were treated by surgical debridement and antibiotics, and four were treated by antibiotics alone. Eleven infections were cleared with treatment, and three patients had recurrent or chronic infections that were treated by antibiotic suppression. The remaining complications were treated in a variety of ways that were consistent with the specific complication. In the comparison group both infections were treated by surgical debridement and antibiotics. Two acute inflammatory reactions in the comparison group were also treated by arthroscopic debridement but were culture negative.

DISCUSSION

Stem cells are a heterogeneous group that can include embryonic stem cells, induced pluripotent stem cells, or mesenchymal or stromal stem cells. The cells can be derived from bone marrow, blood, or adipose tissue and can be harvested from donors or patients directly.[8,10,14,15,22,23] There are many methods for how the cells are treated, concentrated, or manipulated. The diversity of processing methods as well as the lack of reporting of even basic characteristics and composition are barriers to understanding. There is no universally accepted system to allow classification of stem cells. A detailed discussion about the safety and merits of the different cells and preparation methods is beyond the scope of this work.

Stem cells were injected without complications for 92% of the patients in this study and this treatment reduced pain for 71% of the patients for a mean of 17 mo. However, improvement is not proof that stem cells augment or accelerate healing of articular cartilage, and this study did not examine imaging or perform validated assessments of tissue health and joint function. The complication rate among patients who received stem cells was 8%, and the complication rate for patients who received injections of steroids or viscosupplementation was 2%. In a meta-analysis of controlled multicenter studies of 1767 patients, serious complications (e.g., hospitalization, persistent disability) after intraarticular steroid injection and placebo injection occurred in three to four out of 1000 patients. The overall complication rate in the present study was consistent with the findings of this meta-analysis.[24–26] Tumor formation and infection are serious complications. The frequency of complications was comparable for patients receiving autologous and donated stem cells. Most other studies of stem cells report few, if any, complications. There have been several concerns from the FDA and medical regulators about making the necessary disclosures and providing necessary follow-up.[14,21]

The incidence of serious local complications in this study was higher with a statistical significance ($P<0.001$) in patients who were treated with stem cells than with viscosupplementation or steroids. The incidence of systemic reactions, such as syncope and arrhythmia, was also higher with stem cells than with other injections.[12,23,24,27,28] Stem cells have been described as proarrhythmic.[23] The development of local-tissue reactions and new allergies is consistent with any challenge to the immune system and has been reported previously with stem-cell therapy.[29] The development of neoplasms is not unexpected, but previously it has not been reported in joints. It is consistent with the basis of how stem cells are expected to work and has been reported occasionally in other tissues. Stem cells, particularly embryonic, have tumorigenic potential and have been proposed as a basis for neoplasm. Embryonic stem cells form teratomas when injected into mice. Murine neural stem cells can transform into malignant gliomas with minimal genetic changes. Furthermore, rapidly dividing cells in culture can acquire mutations that could predispose to neoplastic transformation.[19,29,30] Very serious tumors in other tissues have developed in the context of stem-cell tourism.[14,20,29,30]

Neoplasm development illustrates an extremely serious complication of introducing stem cells into patients. Investigators have attempted to reduce the risk of stem-cell-related tumors in controlled clinical trials by means of maturing the pluripotent stem cells in vitro into postmitotic phenotypes before administration.[31] The current FDA directive to provide stem cells with only minimal manipulation reduces the concentration and numbers of cells injected. This decreases the efficacy of stem cells and reduces the neoplastic potential, but as was shown in this study, it does not provide complete safety.

Injecting stem cells affects the immune system. The injection can induce a direct immune response or indirectly induce an upregulation of an immune response. Also, it may have a downregulation effect on the immune system. An immune suppressive and antiinflammatory effect of stem cells in arthritis has been observed. The immunogenicity of stem cells remains unpredictable. A rare instance of a latent viral reaction or new allergy along with signs of chronic joint inflammation is not surprising and has been reported.[10,18,23,32] When stem cells are removed from a donor or patient and they undergo some degree of processing, there is a chance of viral, particulate, or microbial contamination. There were more infections and instances of chronic effusion with stem cells than typically seen with other injections, but synovitis-mimicking infection has also been reported with injections of viscosupplementation.[33–35] It is important to recognize that the treated joints were not normal and their resistance to infection was lower when compared with a normal joint.

The safety and efficacy of stem cells that have been derived from peripheral blood or bone marrow for hematopoietic reconstitution are well established for cancer therapy. Increasingly, however, hematopoietic stem cells and stem cells that have been derived from adipose tissue are being used to treat multiple orthopaedic, neurologic, and other diseases. Autologous and allogeneic stem cells are being used in practice based

on minimal clinical evidence of safety or efficacy. Stem-cell therapy has been described as "regenerative medicine" to capture the value that proponents claim these treatments have for several medical conditions.[23] Regeneration is not rejuvenation, and a report of improvement is not the same as tissue healing or augmentation.[8,17,23,35] When compared with an oral placebo, an intraarticular placebo is more effective in treating osteoarthritis. Also, intraarticular pharmacologic interventions are more effective than sham injections or saline. Both sham injections and saline also have side effects with 0.4% of patients requiring a hospital admission.[24,25]

The efficacy of stem cells in the long-term relief of joint symptoms was not established by this study. The initial positive response from stem-cell injection was 71%, which is more positive than either placebo, sham injections, or saline. The positive response was usually limited. At final follow-up, 15% of patients were improved, which is similar to the 13% to 17% of patients who improved with no treatment or with saline infusion.[24,25] The improvement that was gained should be balanced against the risks and cost of treatment. The results achieved must also be balanced against the chance of improvement with no treatment, sham treatment, or placebo.

Despite the absence of compelling evidence from adequate, well-controlled clinical trials, some practitioners assert that stem cells have a unique capacity to restore health because they can sense their environment and differentiate in a manner that repairs any defect. A separate argument is that conducting controlled trials and meeting regulatory standards for such promising therapies would be too complex and take too long. Therefore, clinical practice should not wait for studies or perform their own studies before providing stem cells to patients in need. Proponents of both arguments generally assert that stem-cell therapies are quite safe, particularly when the cells are derived from an autologous source.[11,15,16,31,36] However, in this study autologous and allogeneic stem cells had an equal rate of complications.

For treatments that provide an impressive benefit to patients, the FDA does not require larger studies than those that are needed to prove that benefits outweigh risks. When benefits are dramatic, trials for regulatory approval can be sized modestly. For example, a statistically significant 100% improvement in an outcome measure could be detected in a randomized trial involving as few as 42 participants.[21]

Cell-based therapies that use autologous injected stem cells have attractive features: a perfect genetic match, localization to the site of need, and nonsystemic application. Stimulating the differentiation of one's own cells by means of easily deliverable cells is more attractive than using invasive microfracture or cartilage grafting techniques to stimulate autogenous stem cells to fill in cartilaginous defects. It is easy to capture a patient's imagination with a positive message. It is attractive to provide patients with a cartilage or tendon maintenance or regenerative strategy that involves growth factors applied directly to their painful and disabling joint.[11,13,15,17,18]

It is clear from this work that many practitioners providing stem cells are not following their patients long enough or identifying all their complications. Therefore, they are speculating about the safety and efficacy. This undermines scientific rigor and recognized clinical trials. These clinics recently have been described as rogue stem-cell clinics.[37] Stem cells were harmful to 8% of patients in the present study. Dr. Thomas was optimistic about the use of stem cells for indications beyond leukemia but called for careful scientific studies.[8] This work suggests there is an increased need for monitoring stem-cell clinics and regenerative medicine practitioners. Also, there is a need for more detailed patient education about the risks of stem-cell injections. Clinics providing stem-cell therapy should provide extended monitoring and reporting of complications.

Limitations and Future Perspectives

There are limitations to this study. The data were gathered through an administrative data base. However, the documentation for the treatment and complications was complete and was supported by billing records. The identification of complications in this study was not dependent on the treating practitioner who provided the injection. 54% of the complications were identified by subsequent treating physicians. Most other studies come from programs providing stem-cell therapy.

Because the HSA and FSA accounts were associated with employee benefit programs, the study group included patients and their dependents employed by larger companies. This may introduce selection bias. The HSA and FSA accounts followed patients into retirement, however, which allowed for complete follow-up of patients. The data base likely represents a reasonable, albeit younger, cross-section and possibly more affluent segment of society. The cost of stem-cell therapy, however, results in a selection of patients who have the means to pay.

An additional limitation is that the type of stem cells used and method of their preparation and dose was heterogeneous. There are many commercial stem-cell products available. Also, there are many preparation protocols for stem cells, and the treatments are variable. Most published studies do not provide enough information to allow replication, which makes interpretation of the outcome almost impossible. It is beyond the scope of this, and possibly any, study to characterize the very complex data set to entirely define the practice of stem-cell joint injection medicine. This does leave room for programs and practitioners to claim that the findings of the present study do not apply to them. At the same time, it mandates that treating practitioners provide their own data with compelling numbers of patients and sufficient follow-up periods. The stem-cell data in this study came from clinics whose credibility was derived from tokens of scientific legitimacy rather than peer-reviewed publications.[38]

Future studies have been designed to focus on stem-cell clinics. The data collection includes information on the professional standards used in informed consent, advertising, complication surveillance and management, and long-term patient outcomes data. Also, data on the financial policies and practices of the clinics are being collected.

CONCLUSIONS

Stem-cell injections into the knee, hip, and shoulder that are currently being provided have more complications at a significant or highly significant level than steroid or viscosupplementation injections. The complications that are experienced from stem-cell injections result in important

medical events and higher cost. The long-term benefit of stem-cell injections has not been established to justify accepting these risks.

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REFERENCES

1. Jacobson LO, Simmons EL, Marks EK, *et al*. Recovery from radiation injury. *Science*. 1951; 113:510–511.
2. Shi Q, Rafil S, Wu MH, *et al*. Evidence for circulating bone marrow-derived endothelial cells. *Blood*. 1998; 92:362–367.
3. Thomas ED, Lochte HL Jr, Cannon JH, *et al*. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest*. 1959; 38(10 Pt 1-2):1709–1716.
4. Thomas ED, Lochte HL Jr, Lu WC, *et al*. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med*. 1957; 257:491–496.
5. Buckner CD, Epstein RB, Rudolph RH, *et al*. Allogeneic marrow engraftment following whole body irradiation in a patient with leukemia. *Blood*. 1970; 35:741–747.
6. Dedomenico M, Sameh AA, Berger K, *et al*. Experimental coronary artery surgery. Long-term follow-up, bypass venous autografts, longitudinal arteriotomies, and end-to-end anastomoses. *J Thorac Cardiovasc Surg*. 1968; 56:617–623.
7. Thomas ED, Storb R, Clift RA, *et al*. Bone-marrow transplantation (second of two parts). *N Engl J Med*. 1975; 292:895–902.
8. Thomas E. Does bone marrow transplantation confer a normal life span? *N Engl J Med*. 1999; 341:50–51.
9. Clift RA, Thomas ED. Seattle Marrow Transplant Team. Follow-up 26 years after treatment for acute myelogenous leukemia. *N Engl J Med*. 2004; 351:2456–2457.
10. Blau HM, Dale GQ. Stem Cells in the treatment of disease. *N Engl J Med*. 2019; 380:1748–1760.
11. Caulfield T, Sipp D, Murry CE, *et al*. Scientific community: confronting stem cell hype. *Science*. 2016; 352:776–777.
12. Kalb C, Rosenberg D. Stem cell division. *Newsweek*. 2004; 144:42–50.
13. Kim TK. CORR® International-Asia Pacific: stem cell-based treatments in orthopaedic practice-is it ready for primetime in the Asia-Pacifc Region? *Clin Orthop Relat Res*. 2019; 477:695–697.
14. Marks PW, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. *N Engl J Med*. 2018; 378:954–959.
15. Turner L. The US direct-to-consumer marketplace for autologous stem cell interventions. *Perspect Biol Med*. 2018; 61:7–24.
16. Zhao L, Kaye AD, Abd-Elsayed A. Stem cells for the treatment of knee osteoarthritis. A comprehensive review. *Pain Physician*. 2018; 21:229–242.
17. Bunzil S, Obrien P, Ayton D, *et al*. Misconceptions and acceptance of evidence-based nonsurgical interventions for knee osteoarthritis. A qualitative study. *Clin Orthop Relat Res*. 2019; 477:1975–1983.
18. Rickert J. On patient safety: regenerative medicine-the hype amplifies safety concerns. *Clin Orthop Relat Res*. 2019; 477:1566–1568.
19. Srivastava A, Mason C, Wagena E, *et al*. Part 1: Defining unproven cellular therapies. *Cytotherapy*. 2016; 18:117–119.
20. Bowman M, Racke M, Kissel J, *et al*. Responsibilities of health care professionals in counseling and educating patients with incurable neurological diseases regarding "stem cell tourism": caveat emptor. *JAMA Neurol*. 2015; 72:1342–1345.
21. Marks PW, Witten CM, Califf RM. Clarifying stem cell therapy's benefits and risks. *N Engl J Med*. 2017; 376:1007–1009.
22. Broxmeyer HE, Douglas GW, Hangoc G, *et al*. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc Natl Acad Sci USA*. 1989; 86:3828–3832.
23. Macia E, Boyden PA. Stem cell therapy is proarrhythmic. *Circulation*. 2009; 119:1814–1823.
24. Altman RD, Devji T, Bhandari M, *et al*. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. *Semin Arthroplasty Rheum*. 2016; 46:151–159.
25. Jüni P, Hari R, Rutjes AW, *et al*. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Sys Rev*. 2015; 10:CD005328.
26. Kaplan R. Septic Arthritis after intra-articular injection of hydrocortisone. *JAMA*. 1954; 155:597.
27. Bannuru RR, Schmid CH, Kent DM, *et al*. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015; 162:46–54.
28. Kennedy DJ, Schneider B, Casey E, *et al*. Vasovagal rates in fluoroscopically guided interventional procedures: A study of over 8,000 injections. *Pain Med*. 2013; 14:1854–1859.
29. Berkowitz AL, Miller MB, Mir SS, *et al*. Glioproliferative lesion of the spinal cord as a complication of "stem-cell tourism". *N Engl J Med*. 2016; 375:196–198.
30. Hiltzik M. *A gruesome case study points to the hazards of stem cell tourism*. ■: Los Angeles Times; 2019.
31. Herberts CA, Kwa MS, Hermsen HP. Risk factors in the development of stem cell therapy. *J Transl Med*. 2011; 9:29.
32. Hosakoppal SS, Bryce PJ. Transplant-acquired food allergy: current perspectives. *J Allergy*. 2017; 10:307–315.
33. Chen AL, Desai P, Adler EM, *et al*. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee: a report of six cases. *J Bone Joint Surg Am*. 2002; 84:1142–1147.
34. Kim JH, Choi JS, Yun JH, *et al*. Foreign body reaction to injectable hyaluronic acid: late granuloma formation. *Ann Dermatol*. 2015; 27:224–225.
35. Mohamed M, Patel S, Plavnik K, *et al*. A retrospective analysis of septic arthritis caused by intra-articular viscosupplementation and steroid injections in a single outpatient center. *J Clin Med Res*. 2019; 11:480–483.
36. Saltzman BM, Kuhns BD, Weber AE, *et al*. Stem cells in orthopedics: a comprehensive guide for the general orthopedist. *Am J Orthop (Belle Mead NJ)*. 2016; 45:280–326.
37. Murray IR, Chahla J, Frank RM, *et al*. Rogue stem cell clinics. *Bone Joint J*. 2020; 102-B:148–154.
38. Sipp D, Caulfield T, Kaye ■, *et al*. Marketing of unproven stem-cell based interventions: A call to action. *Sci Transl Med*. 2017; 9:eaag0426.