Complications Following Biologic Therapeutic Injections: A Multicenter Case Series

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Purpose: To describe the complications that occur following biologic therapeutic injections. **Methods:** We queried physician members of the Biologic Association, a multidisciplinary organization dedicated to providing a unified voice for all matters related to musculoskeletal biologics and regenerative medicine. Patients included in this study must have (1) received a biologic injection, (2) sustained an adverse reaction, and (3) had a minimum of 1-year follow-up after the injection. Patient demographic information, medical comorbidities, diagnoses, and previous treatments were recorded. The type of injection, injection setting, injection manufacturers, and specific details about the complication and outcome were collected. **Results:** In total, 14 patients were identified across 6 institutions in the United States (mean age 63 years, range: 36-83 years). The most common injections in this series were intra-articular knee injections (50%), followed intra-articular shoulder injections (21.4%). The most common underlying diagnosis was osteoarthritis (78.5%). Types of injections included umbilical cord blood, platelet-rich plasma, bone marrow aspirate concentrate, placental tissue, and unspecified "stem cell" injections. Complications included infection (50%), suspected sterile inflammatory response (42.9%), and a combination of both (7.1%). The most common pathogen identified from infection cases was *Escherichia coli* (n = 4). All patients who had isolated infections underwent treatment with at least one subsequent surgical intervention (mean: 3.6, range: 1-12) and intravenous antibiotic therapy. **Conclusions:** This study demonstrates that serious complications can occur following treatment with biologic injections, including infections requiring multiple surgical procedures and inflammatory reactions. **Level of Evidence:** Level IV, case series.

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Biologic injections, which can be defined as therapeutic injections using products obtained from a human source, have garnered increased attention over the past 2 decades with a specific focus on optimizing translational implementation.[1-3] As the field of regenerative medicine has continued to expand, tremendous gains have been made in exploring and evaluating potential therapeutic applications in the area of musculoskeletal medicine.[4-7] However, despite some advancements in our fundamental understanding and the potential uses of these cell-based injections, these injections have been advertised as having a wide variety of beneficial effects that are often unsubstantiated.[4,8-12] Furthermore, commercial interests and direct-to-patient targeted advertising of unproven, ambiguously defined "stem cells" have not only hindered scientific

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progress but have also directly contributed to patient confusion.[9,10,13,14] This trend has resulted in adverse patient outcomes and poses several ethical questions.[10,11,13]

One of the major issues regarding the clinical use of biologics is the relative lack of regulation, transparency, and standardization across the field.[4,10,11,13] Biologics carry a unique risk if not prepared, sterilized, processed, and administered meticulously, as many of these products have been able to bypass the normally rigorous oversight of the United States Food and Drug Administration through exemptions and off-label use.[9-11,15] Furthermore, as a result of direct-to-consumer advertising, patients are often interested in seeking treatment with these biologics as promising alternatives to traditional therapies for orthopaedic conditions.[11] These variables have contributed to an environment in which the indiscriminate administration of biologic "stem cell" injections has become prevalent.[4]

This topic became a subject of national news when, in 2018, several patients who received injections of umbilical cord blood processed by Genetech, Inc. (San Diego, CA) and distributed by Liveyon, LLC (Yorba Linda, CA) were found to develop infections. This prompted further investigation and testing by the Centers for Disease Control and Prevention, who identified 12 patients who had undergone umbilical cord blood injections for purposes other than hematopoietic or immunologic reconstitution and subsequently developed culture-confirmed infections.[15] Bacteria included *Enterobacter cloacae*, *Citrobacter freundii*, *Escherichia coli*, *Enterococcus faecalis*, and *Proteus mirabilis*.[15] While there were no mortalities, all of these patients underwent hospitalization. Given the severity of the potential adverse events and the atypical nature of the pathogenic organisms causing septic arthritis found in this investigation, it is becoming increasingly important for physicians to be cognizant of the possible complications of biologics to adequately counsel patients about associated risks and to be able to recognize and treat these patients.

Significant efforts are being made to refine transparency and standardization of cell-based biologic therapies.[9,10,13,16] However, the true rates of adverse events and complications following these interventions need to be better elucidated. To date, only a few case reports of adverse responses to these biologic injections have been published in the literature.[8,17] The aim of this study was to describe the complications that occur following biologic therapeutic injections. We hypothesized that the majority of complications would consist of septic arthritis necessitating surgical intervention.

Methods

All physician members of the Biologic Association, a multidisciplinary organization dedicated to providing a unified voice for all matters related to musculoskeletal biologics and regenerative medicine, were contacted via e-mail and asked if they had any patients meeting the inclusion criteria. Inclusion criteria constituted patients who had (1) received a biologic injection, (2) sustained an adverse reaction, and (3) had a minimum of 1-year follow-up. We defined a "biologic injection" as a therapeutic injection using products obtained from a human source, including cellular therapies, platelet-rich plasma, bone marrow aspirate concentrate, adipose-derived products, and any placental, umbilical cord, or amniotic products. Members of the Biologic Association also disseminated this query via e-mail to colleagues in local and regional networks. The study received approval from the Hospital for Special Surgery institutional review board (January 7, 2019; #2018-2240).

Potential patients were screened by the lead and senior authors, and those meeting the inclusion criteria were added to the study. Data were collected retrospectively, patient demographic information, medical comorbidities, diagnoses, and previous treatments were recorded. The type of injection, injection setting, and injection manufacturers were collected. Information related to the diagnosis of the adverse event and details of the treatment of the complication were also recorded. A complete list of the information collected for each patient is listed in Table 1.

Deidentified patient data were extracted and analyzed by 1 of 2 authors (C.D.E., D.A.N.). Patients were considered to have infections only if there were positive culture results confirming the diagnosis. Data were stored, and basic calculations were performed using Microsoft Excel; 2018 (Microsoft, Redmond, WA). Comparative group analysis for time from injection to time of presentation was calculated using 2-tailed Student t test, and all analysis was performed using SPSS Statistics 22; 2018 (IBM Corp., Armonk, NY). The significance level was $P = .05$ for all statistical analyses.

Results

A total of 14 patients treated in 6 institutions across the United States were identified as meeting the inclusion criteria. Patients who did not sustain an adverse reaction or had less than 1-year follow-up were excluded. There were 11 male patients and 3 female patients. The mean patient age was 63 years (range, 36-83 years). The average patient body mass index was 27.3 (range, 19.7-38.9).

Overall, the patients included in the study had few medical comorbidities that would put them at risk of infection or inflammatory reaction. None of the patients reported a history of diabetes mellitus. No patients had a history of chronic steroid use or known immunosuppressive disorders. Three patients reported a remote history of smoking—all 3 had quit at least 30 years before presentation—and there were no active

Table 1. List of Data Collected: Patient Information, Biologic Administered, Details, and Treatment of Adverse Event

Patient information
Patient age
Patient BMI
Underlying diagnosis
Existing joint pathology
History of diabetes (HgbA1c)
Comorbidities
Current medications
Smoking history
Prior treatments
Biologic administered
Description of biologic administered
Volume of dose administered
Anatomic location where biologic administered
Manufacturer of biologic
Route of administration
Details of adverse event
Patient's symptoms at presentation
Time between treatment and presentation of adverse response
CBC
ESR
CRP
Lactate
Culture results
Imaging studies
Pathology reports
Treatment of adverse event
Antibiotics administered
Surgical procedures performed
Outcome of treatment

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HgbA1c, hemoglobin A1c.

smokers. One patient reported a history of a previous autoimmune disorder (autoimmune encephalitis), and this patient developed a suspected inflammatory reaction. One patient had a history of a previous severe systemic infection (*Klebsiella sepsis*), and this patient developed *Escherichia coli* septic arthritis.

The most common underlying diagnosis was osteoarthritis (78.5%). Other underlying diagnoses included myofascial pain, Achilles tendinopathy, and low back pain (Table 2). The majority of patients (8 of 14) had had no previous treatments for their condition. Three patients had received a previous nonbiologic injection, such as hyaluronic acid or a corticosteroid injection. Two patients had undergone previous surgical intervention for their condition, and one patient had received a previous biologic injection identified as an adipose-derived "stem cell" treatment.

The most common site of injection in this series was the knee (50%), followed by the shoulder (21.4%). One patient received both shoulder injections and a knee injection, and one patient received an intra-articular hip injection (Table 2). In total, 12 of the 14 patients received intra-articular injections, whereas 2 patients received injections in muscle (paraspinal musculature) or tendon (Achilles tendon) (Table 3).

The majority of the patients in this series (12 of 14, 85.7%) received injections in clinics outside of the institution to which they presented for treatment of their complication. All of the patients who developed infections (n = 8) received injections at outside institutions. Complications included infection (50%), suspected sterile inflammatory response (42.9%), and a combination of both infection and inflammatory response (7.1%). Mean time from injection to time of presentation of the adverse response was 8.9 days (range, 3 hours to 30 days). There was no significant difference in time from injection to presentation between those diagnosed with septic arthritis versus those diagnosed with an inflammatory reaction. Of the patients who were diagnosed with infections, the most common injection type administered was umbilical cord blood (n = 3), and the most common pathogen identified was *E. coli* (n = 4) (Table 2). All patients who had isolated infections underwent treatment with at least 1 surgical intervention and intravenous antibiotic therapy (mean: 3.6 surgeries, range, 1-12) (Table 3). One patient was suspected to have graft-versus-host disease and potentially a concurrent infection. *E. coli* was cultured from blood cultures, but no arthrocentesis was performed. Because no intra-articular culture data were provided, this patient was excluded from the confirmed infection group.

Discussion

The principal finding of our study is that the most common complication following biologic injections was infection (50%), which confirmed our hypothesis. Other complications included suspected sterile inflammatory response (42.9%) and a combination of both sterile inflammatory response and infection (7.1%). All of the confirmed infections in this study were cases of septic arthritis, which were verified by culture and pathology data. The most common pathogen identified was *E. coli*, and of the patients who were diagnosed with infections, the most common injection type was umbilical cord blood. Specifically, *E. coli* infections were reported in 3 patients who had received injections of umbilical cord blood and 1 patient who had received an injection of "placental stem cells." In addition, 1 patient who received an unknown "stem cell" injection subsequently developed *E. coli* sepsis.

In recent years, there has been increased interest in biologic injections and cell-based therapies.[18,19] While biologics may have significant potential in the treatment of orthopaedic conditions, there is currently little standardization and regulation of how these biologic therapies are obtained, processed, and screened.[4,10] Furthermore, although previous studies have suggested there are low rates of adverse reactions following autologous cell treatments for orthopaedic conditions, little is known about the complications that can arise

Table 2. Patient Diagnoses, Previous Treatments, Complications, and Pathogens From Infections

	Number of Patients	Percentage of Patients
Underlying diagnosis		
Osteoarthritis	11	78.5%
Myofascial pain	1	7.1%
Achilles tendinopathy	1	7.1%
Low back pain	1	7.1%
Previous treatments		
No previous treatment	8	57.1%
Previous nonbiologic injection (i.e., HA, CSI)	3	21.4%
Previous surgical intervention	2	14.3%
Previous biologic injection (i.e., adipose-derived "stem cell" injection)	1	7.1%
Injection Site		
Knee (intra-articular)	7	50.0%
Shoulder (intra-articular)	3	21.4%
Knee and shoulder (intra-articular)	1	7.1%
Hip (intra-articular)	1	7.1%
Muscle/tendon	2	14.3%
Complications		
Infection	7	50.0%
Suspected inflammatory response	6	42.9%
Infection and inflammatory response	1	7.1%
Pathogens from isolated infections*		
Escherichia coli	4	57.1%
Staphylococcus epidermidis	1	14.3%
Methicillin-sensitive *Staphylococcus aureus*	1	14.3%
Citrobacter	1	14.3%

CSI, corticosteroid injection; HA, hyaluronic acid.

*All patients with isolated infections (n = 7) underwent treatment with at least one subsequent surgical intervention and intravenous (IV) antibiotic treatment.

after allogeneic cell-based therapies.[20] As indiscriminate administration of biologic "stem cell" injections has become prevalent, it is important that both physicians and patients are fully informed of the risks involved with these treatments. This study demonstrates that serious infections and/or inflammatory reactions can

Table 3. Details of Patient Injections, Adverse Events, and Pathogens

Patient	Age	Sex	Injection Description	Manufacturer	Injection Site	Adverse Event	Pathogen
1	78	M	Placental stem cells	Biogenix/ GenCure	Bilateral knees	Septic arthritis	*E. coli*
2	83	M	Umbilical cord blood	Genetech, Inc.	Bilateral shoulders	Septic arthritis	*E. coli*
3	57	M	Umbilical cord blood	Genetech, Inc.	Unilateral shoulder	Septic arthritis	*E. coli*
4	65	F	Microfragmented adipose tissue	Lipogems	Bilateral knees	Inflammatory response	N/A
5	51	F	Amniotic fluid	Unknown	Unilateral knee	Septic arthritis	*Citrobacter*
6	69	M	Stem cell	Genetech, Inc.	Bilateral shoulders, unilateral knee	GVHD, sepsis	*E. coli*
7	65	M	Lipoaspirate	Unknown	Unilateral knee	Septic arthritis	*Staphylococcus epidermidis*
8	44	F	PRP	Unknown	Bilateral shoulders	Septic arthritis	MSSA
9	73	M	BMAC	Arthrex Angel System	Bilateral knees	Inflammatory response	N/A
10	67	M	Umbilical cord blood	Unknown	Bilateral knees	Inflammatory response	N/A
11	65	M	Amnion membrane	Amniofix	Achilles tendon	Inflammatory response	N/A
12	62	M	Umbilical cord blood	Genetech, Inc.	Unilateral hip	Septic arthritis	*E. coli*
13	70	M	Placental tissue + PRP	Unknown	Unilateral knee	Inflammatory response	N/A
14	36	M	Wharton's jelly + PRP	Invitrx	Paraspinal musculature (multiple sites)	Inflammatory response	N/A

BMAC, bone marrow aspirate concentrate; F, female; GVHD, graft-versus-host disease; M, male; PRP, platelet-rich plasma; MSSA, methicillin-sensitive *Staphylococcus aureus*; N/A, not applicable.

occur following biologic injections. Future studies are necessary to elucidate the true incidence of these complications and stricter regulations are needed to verify the safety and efficacy of biologics.

Direct-to-consumer marketing of unapproved cell-based therapies has also undoubtedly contributed to the problem.[21] There are hundreds of businesses in the United States alone that engage in direct-to-consumer marketing for "stem cell" interventions and advertise both autologous and allogenic cells treatments.[22,23] Because there is little oversight of these clinics, many make unsubstantiated claims regarding the efficacy of the treatments and downplay the risks involved while also charging substantial out-of-pocket fees.[11,12,21]

Clinical infections following administration of cell-based products has been reported previously.[15] In the 2018 investigation by the Centers for Disease Control and Prevention of the Genentech-processed and Liveyon-distributed umbilical cord blood samples, *E. coli* was isolated from several samples, including unopened vials, which suggests that the contamination occurred before distribution.[15] Therefore, the results from our case series are consistent with this previous report in that umbilical cord blood—derived products have been previously implicated for having contaminants, perhaps due to the lack of validated processes for sterilization, and that *E. coli* has previously been shown to be one of the bacterial contaminants in these products.

Descriptions of noninfectious or suspected inflammatory reactions to biologic injections has been less well-described in the literature.[24,25] This is likely due to the challenging nature of diagnosing these conditions. In the absence of overt infectious signs such as a fever, elevated serum white blood cell, leukocyte cell count on arthrocentesis, and culture data, patients may present with symptoms similar to those of septic arthritis. Interestingly, only 1 patient in this series had a known history of autoimmune disease before receiving a biologic injection. One patient, who is believed to have had a sterile inflammatory reaction, was found to be HLA-B27 positive and diagnosed with HLA-B27 reactive arthritis after undergoing an extensive diagnostic workup.

While the adverse events described in this study are likely rare occurrences, the gravity of the sequelae should not be understated. All patients who had culture-confirmed septic arthritis required at least 1 surgical procedure for irrigation and debridement after the diagnosis had been made, and 4 of the 7 patients required more than 1 surgical procedure. One of the patients in our cohort underwent long-term antibiotic therapy and a total of 12 subsequent surgical interventions over a 15-month period for bilateral shoulder septic arthritis, culminating in bilateral 2-stage reverse shoulder arthroplasty. Furthermore, previous intra-articular infection may be considered a relative contraindication to arthroplasty, as the history of infection in the joint likely increases the risk of postoperative infection following arthroplasty.

Limitations

While the current study constitutes a relatively large series of complications following biologic injections, our search was not comprehensive. Because we were unable to determine the total population of patients who have received biologic therapeutic injections, we cannot estimate the overall incidence of complications that occur following these injections. This is in part complicated by the fact that many of these injections are taking place in "stem cell clinics" with limited or poor oversight. Notably, all of the patients in this series received injections at outside facilities before seeking care at the institutions included in our review. In addition, while we collected as much data as possible regarding the details of the specific injections administered, some of the companies used were unavailable to us. Because of the large number of companies available and the wide variety of injections used, we were unable to elucidate whether a specific type of injection or a specific company had more adverse events than other manufacturers. Finally, there is the possibility that some of the pathogens identified in this series are indicative of a contaminant rather than a true infection. For example, one patient had cultures that grew *Staphylococcus epidermidis*, a micro-organism which is a major component of the normal skin flora. However, in this particular case, intraoperative pathology was consistent with septic arthritis.

Conclusions

This study demonstrates that serious complications can occur following treatment with biologic injections, including infections requiring multiple surgical procedures and inflammatory reactions.

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