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# Current use of biologic therapies for musculoskeletal disease: A survey of board-certified equine specialists

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## Abstract

**Objective:** To evaluate the use of mesenchymal stem cells (MSCs), autologous conditioned serum (ACS), platelet-rich plasma (PRP), and autologous protein solution (APS) for the treatment of equine musculoskeletal disease by diplomates of the American College of Veterinary Surgery (ACVS), and American College of Veterinary Sports Medicine and Rehabilitation (ACVSMR).

**Study design:** Cross-sectional study.

**Sample population:** Diplomates ($n = 423$).

**Methods:** An email link was sent to ACVS and ACVMR diplomates. A survey contained 59 questions regarding demographics, as well as indications, frequency, adverse effects, and limitations of use. Responses were analyzed using Fisher's exact test.

**Results:** One hundred and fifty four surveys were analyzed. Years in practice and type of practice were not associated with biologic therapy use. PRP was the most used therapy (120/137; 87.5%). PRP and MSCs were most often administered intralesionally while ACS and APS were most often administered intra-articularly. ACS (50/104; 48.1%) treatment was repeated commonly within 2 weeks of initial injection. MSCs (39/90; 43.3%) and PRP (38/100; 38%) were commonly repeated 1-2 months after initial injection and APS was typically repeated >4 months after initial injection (21/53; 39.6%). Local inflammation and expense were the most common adverse effect and limitation of use.

**Abbreviations:** MSCs, mesenchymal stem cells; ACS, autologous conditioned serum; PRP, platelet rich plasma; APS, autologous protein solution; ACVS, American College of Veterinary Surgery; ACVSMR, American College of Veterinary Sports Medicine and Rehabilitation.

Some results of this study were presented at the AO Foundation Virtual Symposium - Bridging the Gap: Translating Clinical Research to Clinical Practice (December 7, 2020), and the North American Veterinary Regenerative Medicine Association Conference (September 22 - 24, 2021) in Fort Collins, Colorado.

**Conclusion:** Diplomates most commonly utilized PRP and MSC intralesionally for soft-tissue injuries, and ACS and ACP intra-articularly for joint injury. Protocols for repeated administration varied widely. Local inflammation was a clinical concern with the use of biologics.

**Clinical significance:** Biologic therapies are used commonly by ACVS and ACVSMR diplomates for soft tissue and joint disease.

## 1 | INTRODUCTION

Multiple biologic therapies are available for the treatment of equine musculoskeletal disease. Several research studies have investigated the safety and efficacy of mesenchymal stem cells (MSCs),[1–5] platelet-rich plasma (PRP),[6–9] autologous conditioned serum (ACS),[10–12] and autologous conditioned protein (APS).[13] However, limited information is available regarding the use of these products in equine clinical practice. Biologic therapies are defined by the National Institutes of Health as treatments that use substances made from living organisms to treat disease. These substances may occur naturally in the body or may be made in a laboratory (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biological-therapy). While under the jurisdiction of the Food and Drug Administration (FDA), these therapies do not come with a label for approved conditions, dosage, and route of administration, unlike medications which have been previously approved by the FDA. As such, the methods for use of biologic therapies may vary significantly amongst veterinarians. Understanding the use of biologic therapies amongst large-animal veterinarians will provide valuable information for the design and execution of future experimental and clinical studies. Previous surveys of equine practitioners have focused on intra-articular administration of biologic therapies in addition to non-biologic therapies, including polysulfated glycosaminoglycan, hyaluronic acid, and steroid therapies.[14–16] The use of biologic therapies amongst other rehabilitation techniques has also been assessed.[17] The authors are unaware of a single, comprehensive study focusing on the use of biologic therapies by equine practitioners for musculoskeletal skeletal disease including soft tissue conditions, joint conditions, and postoperative management.

The intent of this study was to provide a targeted analysis of the use of biologic therapies for equine musculoskeletal disease by large animal diplomates of the American College of Veterinary Surgery (ACVS) and American College of Veterinary Sports Medicine and Rehabilitation (ACVSMR). Large animal diplomates of the ACVS and ACVSMR were chosen to sample veterinarians with a uniform minimal level of training in musculoskeletal disease and lameness. The objectives of this study were to document the use of biologic therapies (MSCs, ACS, PRP, APS) by large animal diplomates of ACVS and ACVSMR for the treatment of equine musculoskeletal disease to identify the primary reason for the selection of biologic therapies, the route of administration, common indications for use, preferred protocols for repeated injection, users' perceived efficacy, adverse effects, and limitations for use of these products.

## 2 | MATERIALS AND METHODS

### 2.1 | Survey design

The survey population included all large animal diplomates of the ACVS and the ACVSMR with an active email addresses available through the ACVS or ACVSMR website. The biologic therapies evaluated in this survey were MSCs, PRP, ACS, and APS. Questions included respondent demographics, frequency of use, indications of use, adverse effects, limitations of use, dosing intervals and perceived efficacy. Initial questions regarding whether stem cells are used by the respondent included the ability to specify between bone–marrow-derived MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs), or other MSC sources. For all other questions, MSCs were grouped together as a single category without specifying their tissue of origin. Questions related to demographics of the respondents included their years in practice, practice type, practice focus, and board certification type (ACVS and/or ACVSMR). All practitioners were considered as anonymous individuals, and no attempt to group respondents by hospital or practice group was made. For questions regarding indications for use, route of administration, adverse effects, conditions treated, and limitations of use, diplomates were able to select all answers that applied. Diplomates were also given an opportunity to select "other" and provide an alternative answer for questions regarding adverse effects and limitations of use.

## 2.2 | Institutional review board approval

This study and survey materials were approved by the Michigan State University human research protection program (STUDY0003784). In the email correspondence, participants were informed that the survey was entirely voluntary; the participant could refuse to answer certain questions or discontinue participation at any time without consequence. In addition, participants were informed that participation and responses to the study would remain anonymous and only researchers and the institutional review board (IRB) would have access to study responses. All participants were informed that the study would take approximately 15 min to complete, and the results were intended for publication.

## 2.3 | Development and pretesting

The survey was developed by 4 co-authors (AC, LK, LG, WM). The survey was evaluated by 5 individuals, who did not include the investigators. This feedback was used to modify questions to be easier to answer, with improved clarity. The final survey consisted of 59 multiple-choice and rank-order questions.

## 2.4 | Recruitment process

Only those invited could respond to the survey. The initial contact for all potential participants was made via email. The researchers did not advertise the study and no announcement was made prior to the email.

## 2.5 | Survey administration

An email link to an electronic survey was distributed using Survey Monkey (www.surveymonkey.com) between February 1 and April 30, 2020. If survey requests were left incomplete or partially completed, additional anonymous prompts were automatically sent by Survey Monkey every 7 days during the survey period. The survey was voluntary, and no incentives were offered. Approaches such as randomization of questions or adaptive questioning were not used. All participants received the same survey in the same order except when some positive responses led to new questions. The questionnaire was administered over 8 pages with up to 15 questions per page. Participants could scroll backwards and change their answers if desired. Respondents could elect to answer any or all questions such that completion of each question was not required to continue through the survey. If a respondent did not use a particular biologic therapy, questions regarding this therapy were automatically skipped.

## 2.6 | Response rates

A unique visitor was determined by IP address. Response rate was defined as the number of survey participants divided by the number of all eligible respondents contacted. Completion rate was defined as the ratio of unique users who finished the survey versus unique users who started the survey.

## 2.7 | Statistical analysis

As respondents could continue through the survey without completing all questions, each question was reported separately with responses recorded per question. Statistical analysis to investigate the association between predictors (years in practice, practice type) and use of biologic therapies was performed using a Fisher's exact test. Estimation of effect size was conducted by risk ratio with the category as the reference selected based on preference of the authors.

If limited responses were recorded in specific categories, categories were combined for statistical analysis. This occurred when analyzing years in practice and type of practice as outlined in the results section. For responses indicated as "other" responses were reclassified into provided answers where appropriate, or reported separately.

# 3 | RESULTS

The survey is provided in Appendix S1. Information regarding perceived efficacy of these biologic therapies is provided in Appendix S2.

Reporting of this study was guided by the Checklist for Reporting Results of Internet E-Surveys (CHERRIES)[18] and the Veterinary Statement on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE-VET)."[19]

## 3.1 | Response rate

Four hundred and thirty two diplomates were contacted via email between February 1 and April 30, 2020. Three hundred Diplomates opened the email. The response rate was 35.6% (154/432) of the diplomates contacted via

email. Of those who participated in the survey, the completion rate was 86% (133/154).

## 3.2 | Demographics

When questioned about years in practice, respondents were categorized into the following groups: <5 years in practice, 5-10 years, 10-20 years, and >20 years. Only a small number of respondents were in practice less than 5 years (2/153); these responses were therefore recategorized as being in practice <10 years or >10 years for statistical analysis. Eighty percent of the respondents had been in practice for more than 10 years (123/153). Years in practice were not associated with use of biologic therapies (Table 1). Most respondents were ACVS diplomates only (123/154, 79.8%). ACVSMR diplomates accounted for 4.5% (7/154) and diplomates of both ACVS and ACVSMR accounted for 15.5% (24/154). Forty-six percent of respondents (70/151) worked in equine-only private practice positions; 26% (39/151) of respondents worked in academic equine-only positions, and 25% (38/151) of respondents worked in academic large-animal practice. Other practice types reported were private practice mixed-animal practice (1/151), private practice large-animal practice (1/151), combination

**TABLE 1** Summary of respondents ($n = 151$) who indicated use of each biologic therapy, based on years in practice and practice type

| ADMSCs: | Never use | Confirmed use | Total respondents | Risk ratio | Fisher's exact *P* value |
|---|---|---|---|---|---|
| >10 years of practice | 94 (62%) | 27 (18%) | 151 | 1 | $P = .20$ |
| <10 years of practice | 27 (18%) | 3 (2%) | | 0.45 | |
| Academic | 67 (45%) | 11 (7%) | | 1 | $P = .1$ |
| Private practice | 53 (36%) | 18 (12%) | | 1.8 | |
| BMDMSCs: | | | | | |
| >10 years of practice | 35 (23%) | 86 (57%) | 151 | 1 | $P = .65$ |
| <10 years of practice | 7 (5%) | 23 (15%) | | 1.08 | |
| Academic | 23 (15%) | 55 (37%) | | 1 | $P = .50$ |
| Private practice | 17 (11%) | 54 (36%) | | 1.08 | |
| PRP: | | | | | |
| >10 years of practice | 13 (10%) | 93 (69%) | 135 | 1 | $P = .76$ |
| <10 years of practice | 4 (3%) | 25 (19%) | | 0.98 | |
| Academic | 8 (6%) | 60 (45%) | | 1 | $P = 1.0$ |
| Private practice | 8 (6%) | 57 (43%) | | 0.99 | |
| ACS: | | | | | |
| >10 years of practice | 23 (18%) | 80 (61%) | 131 | 1 | $P = .44$ |
| <10 years of practice | 4 (3%) | 24 (18%) | | 1.1 | |
| Academic | 18 (14%) | 48 (37%) | | 1 | $P = .05$ |
| Private practice | 8 (6%) | 56 (43%) | | 1.2 | |
| APS: | | | | | |
| >10 years of practice | 53 (40%) | 50 (38%) | 131 | 1 | $P = .40$ |
| <10 years of practice | 17 (13%) | 11 (8%) | | 0.81 | |
| Academic | 40 (31%) | 26 (20%) | | 1 | $P = .11$ |
| Private practice | 29 (22%) | 35 (27%) | | 1.39 | |

*Note*: Significant relationships were determined via Fisher's exact tests. Significance was set at $P < .05$.

Abbreviations: ACS, autologous conditioned serum; ADMSC, adipose derived mesenchymal stem cells; APS, autologous conditioned protein solution; BMDMSC, bone–marrow-derived mesenchymal stem cells; PRP, platelet-rich plasma.

**TABLE 2** Use of biologic therapies and route of administration used by large animal specialists. The percentage of respondents who used the specified biologic therapy at least once per year (number of respondents who use the modality at least once per year/total number of respondents for that treatment). Respondents were asked to indicate if they administer biologic therapies intra-articularly, intralesionally, intravenously or by another route. Respondents could choose more than 1 method of administration for each biologic therapy

| Biologic Therapy | Percentage of respondents using therapy at least once/year | Intra-articular | Intra-lesional | Intravenous | Other |
|---|---|---|---|---|---|
| ADMSCs | 30/154 (19.5%) | 83/153 (54%) | 117/153 (76%) | 45/153 (29%) | 19/153 (12%) |
| BMDMSCs | 111/154 (72.1%) | | | | |
| PRP | 120/137 (87.5%) | 80/118 (68%) | 115/118 (97%) | 5/118 (4%) | 17/118 (14%) |
| ACS | 106/133 (79.7%) | 104/106 (98%) | 16/106 (15%) | 5/106 (5%) | 8/106 (8%) |
| APS | 61/132 (46.2%) | 61/133 (46%) | 22/133 (17%) | 3/133 (2%) | 1/133 (<1%) |

Abbreviations: ACS, autologous conditioned serum; ADMSC, adipose-derived mesenchymal stem cells; APS, autologous conditioned protein solution; BMDMSCs, bone–marrow-derived mesenchymal stem cells; PRP, platelet-rich plasma.

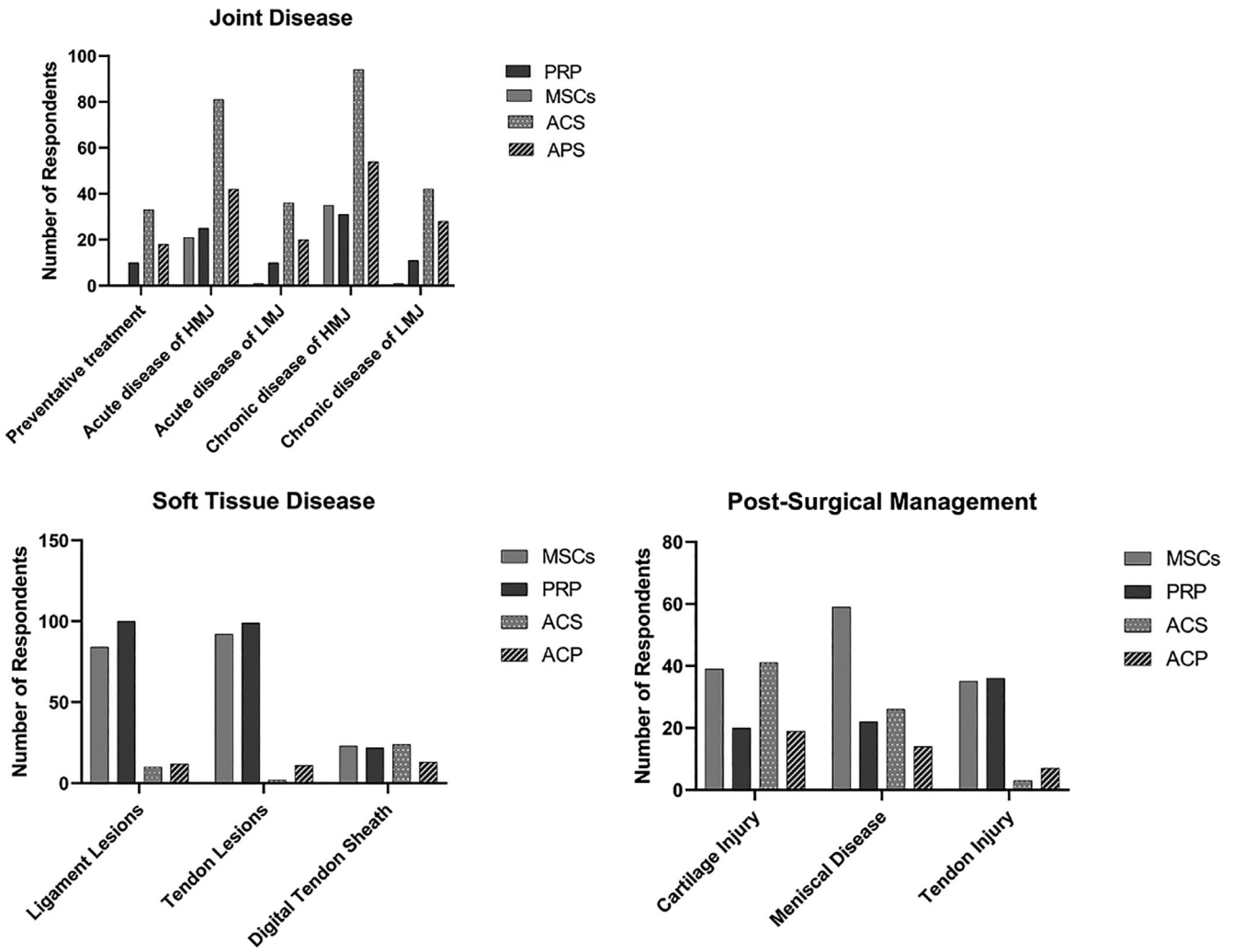


**FIGURE 1** The number of respondents who utilize mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), autologous conditioned serum (ACS), and autologous conditioned protein (APS), by condition. Categories include joint disease (ADHMJ = acute disease high motion joint, ADLMJ = acute disease low motion joint, CDHMJ = chronic disease high motion joint, ADHMJ = acute disease high motion joint), soft tissue disease (tendon lesion, ligament lesion, digital tendon sheath applications), and postsurgical management (cartilage disease, meniscal disease, tendon injury)

equine academic and private practice (1/151), and academic research (1/151). Data were compressed for statistical analysis into respondents who worked in private practice or academic practice. Practice type (academic vs. private practice) had no association with the use of biologics (Table 1).

The most common type of horses treated were sport horses (dressage, show jumping, eventing, polo) (67/152, 44%), followed by western performance horses (cutting, reining, working cow, rodeo) (37/152, 24%), racehorses (23/152, 15%), recreational/pleasure horses (13/152, 9%), and show horses (western pleasure, saddles seat, english pleasure, halter horse, pleasure driving) (12/152, 8%).

## 3.3 | Frequency of use and reasons for use

When asked the primary reason for choosing biologic treatments, 56% (86/153) of respondents based their choice on scientific articles and data showing the efficacy of the product. Twenty percent (30/153) selected biologic therapies based on personal experience, and 10% (15/153) due to previous treatments being ineffective. Five percent (8/153) chose to use biologic therapies based on client request, 2% (3/153) chose a biologic therapy due to access to equipment, 2% (3/153) used biologic therapies as a corticosteroid alternative and <1% (1/153) due to ease of use. Four percent of respondents indicated that they infrequently use biologic therapies.

Platelet-rich plasma was the most commonly used biologic therapy by respondents (87.5%,120/137), followed by ACS (79.7%, 106/133), bone–marrow-derived mesenchymal stem cells (BMDMSCs) (72.1%, 111/154), APS (46.2%, 61/132) and ADMSCs (19.5%, 30/154) (Table 2). Twenty-four percent (37/153) of respondents indicated that they used stem cells that were not adipose-derived or bone-marrow derived, but the cell source was not specified.

## 3.4 | Route of Administration

Respondents were asked to indicate methods of administration for each biologic therapy. Each respondent could indicate multiple methods of administration for the same biologic therapy. The largest number of respondents administered MSCs and PRP intralesionally, while the largest number of respondents administered ACS and APS intra-articularly (Table 2). The musculoskeletal conditions for which respondents utilize MSCs, PRP, ACS, and APS are listed in Figure 1.

**TABLE 3** Percentage of respondents who repeated injections of specific biologic therapies (number of respondents who repeat each treatment/total number of respondents for that treatment)

| Biologic therapy | Frequency of repeated administration (% of row) | | | | |
|---|---|---|---|---|---|
| | Never | Rarely | Commonly | Almost always | Always |
| MSCs | 48/153 (31.4%) | 75/153 (49.0%) | 20/153 (13.1%) | 8/153 (5.2%) | 2/153 (1.3%) |
| PRP | 14/118 (11.9%) | 58/118 (49.2%) | 37/118 (31.4%) | 8/118 (6.8%) | 1/118 (<1%) |
| ACS | 1/106 (<1%) | 11/106 (10.4%) | 44/106 (41.5%) | 28/106 (26.4%) | 22/106 (20.8%) |
| APS | 71/126 (56.4%) | 24/126 (19.0%) | 27/126 (21.4%) | 4/126 (3.2%) | 0/126 (0%) |

Abbreviations: ACS, autologous conditioned serum; APS, autologous conditioned protein solution; MSC, mesenchymal stem cells; PRP, platelet-rich plasma.

**TABLE 4** Percentage of respondents who utilized specific protocols for repeated injection (number of respondents who utilize the protocol/total number respondents for that treatment)

| Biologic therapy | Within 2 weeks of initial injection | Between 2-4 weeks of initial injection | 1-2 months following initial injection | 2-4 months following initial injection | >4 months following initial injection |
|---|---|---|---|---|---|
| MSCs | 1/90 (1.1%) | 30/90 (33.3%) | 39/90 (43.3%) | 10/90 (11.1%) | 10/90 (11.1%) |
| PRP | 8/100 (8%) | 33/100 (33%) | 38/100 (38%) | 15/100 (15%) | 6/100 (6%) |
| ACS | 50/104 (48.1%) | 44/104 (42.3%) | 3/104 (2.9%) | 3/104 (2.9%) | 4/104 (3.9%) |
| APS | 2/53 (3.8%) | 8/53 (15.1%) | 11/53 (20.8%) | 11/53 (20.8%) | 21/53 (39.6%) |

Abbreviations: ACS, autologous conditioned serum; APS, autologous conditioned protein solution; MSCs, mesenchymal stem cells; PRP, platelet-rich plasma.

**TABLE 5** Factor most influencing limitation of use for each biologic therapy, and negative effects following administration of biologic therapies. For limiting factors, respondents were asked to select 1 option. The table also outlines the number of respondents who have encountered negative effects associated with the use of each given biologic therapy. Respondents were able to select multiple outcomes for negative effects

| | **Limitations for use** | | | | **Negative effects** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Biologic Therapy** | **Expense** | **Inconvenience** | **Limited access to equipment** | **Negative personal experience** | **Local inflammation at injection site** | **Systemic inflammation** | **Infection at injection site** | **Systemic infection** | **Other** |
| MSCs | 101/138 (73.1%) | 6/138 (4.3%) | 2/138 (1.4%) | 6/138 (4.3%) | 112/135 (83.0%) | 7/135 (5.2%) | 12/135 (8.9%) | 0/135<br>0% | Venous thrombosis (1)<br>Mineralization (1)<br>Hepatitis (1) |
| PRP | 65/116 (56.0%) | 8/116 (6.9%) | 3/116 (2.6%) | 9/116 (7.8%) | 98/114 (86.0%) | 1/114 (<1%) | 5/114 (4.4%) | 0/114<br>0% | Soft tissue scarring (1)<br>Worsening of lesion (1) |
| ACS | 70/106 (66.0%) | 20/106 (18.9%) | 4/106 (3.8%) | 7/106 (6.6%) | 64/98 (65.3%) | 0/98 (0%) | 5/98 (5.1%) | 0/98<br>0% | None |
| APS | 46/61 (75.4%) | 1/61 (1.6%) | 5/61 (8.2%) | 2/61 (3.3%) | 44/80 (55%) | 0/80 (0%) | 2/80 (2.5%) | 0/80<br>0% | None |

Abbreviations: ACS, autologous conditioned serum; APS, autologous conditioned protein solution; MSC, mesenchymal stem cells; PRP, platelet-rich plasma.

### 3.5 | Repeated Injection and Injection Protocols

Eighty-nine percent of respondents who utilized PRP indicated they frequently repeat injections. In contrast, respondents only repeated injections of APS, MSC, and PRP in 25% (31/126), 20% (30/153), and 40% (46/118) of cases, respectively (Table 3). If respondents performed repeated injections with biologic therapies, they were asked to identify their preferred frequency for each biologic therapy (Table 4). Treatment with MSCs (39/90, 43.3%) and PRP (38/100, 38%) were most commonly repeated 1-2 months following the initial injection. In contrast, treatment with ACS was most commonly repeated within 2 weeks of initial injection (50/104, 48%) or 2-4 weeks following the first injection (44/104, 42%). Respondents repeated APS injections most commonly more than 4 months after the initial injection (21/53, 40%).

### 3.6 | Limitations for use and negative effects

The most common limiting factor for the use of all biologic therapies was expense (Table 5). The percentage of respondents who reported experiencing negative effects after administration of MSCs, PRP, ACS, and APS were 56% (84/151), 59% (70/118), 42% (44/106), and 20% (24/122) respectively (Table 5). Local inflammation was the most commonly reported adverse effect following the use of biologic therapies, followed by local infection at the site of injection. The frequency of negative effects encountered by respondents is presented in Table 5.

## 4 | DISCUSSION

As far as the authors are aware, this is the first survey regarding biologic therapies to collect a representative sample of a targeted group of individuals with a defined level of training. The current study confirmed the widespread use of biologic therapies amongst this group of ACVS and ACVSMR diplomates. Platelet-rich plasma was identified as the most commonly used biologic therapy, with both PRP and MSCs frequently used to treat tendon and ligament lesions. ACS and APS were more commonly used intra-articularly. Additionally, protocols for repeated administration varied widely amongst respondents, indicating a need for further investigation of these products to determine optimal administration intervals. Local inflammation at the site of injection was the most common negative effect noted with any of the biologic therapies (55%-86%), the percentage of respondents who had experienced local infection at the site of injection (2%-9%) is noteworthy. Scientific data showing efficacy was the main reason respondents chose to use biologic therapies and cost of these products was identified as the major limiting factor for use.

Collectively, our study and previous studies revealed an increasing use of biologic therapies. In 2009, 54% of respondents to an electronic survey of equine practitioners indicated they had used ACS.[15] In 2018, an international study of rehabilitation modalities by equine veterinarians suggested an increase in biologic therapy use, with a large majority of respondents using ACS (81%) or PRP (87%).[16] Our study suggested a similar level of use amongst large animal specialists, irrespective of their duration in practice or practice type. This increased use may be attributed to increased commercial availability and advertisement of biologic products coupled with extensive literature surrounding the use of biologic therapies for musculoskeletal disease.[20]

Platelet-rich plasma was the most widely used biologic therapy by large animal diplomates. Despite the differences in survey populations, our study and Velloso et al. (2020) indicated that PRP was the most widely used biologic therapy for musculoskeletal disease.[16] This could be due to the user-friendly, stall-side, products that have become commercially available. In contrast, ACS and MSCs are not available stall side and require an incubation period of 24 h and several weeks, respectively. Autologous protein solution also provides the convenience of immediate use. However, this technology is newer than PRP, ACS, or MSCs and requires a specialized centrifuge.

The vast majority of veterinarians indicated that they most commonly administer PRP intralesionally in tendon and ligament lesions. This application is supported by the current experimental and clinical literature.[8,9,21] A study by Romero et al. in 2017 evaluated the effect of intralesional injections with autologous BMDMSCs, ADMSCs or PRP on surgically induced superficial digital flexor tendon lesions, found similar healing outcomes with MSCs versus PRP.[9] In our study, large animal specialists indicated both PRP and MSCs are frequently used for the treatment of tendon and ligament lesions. The respondents also indicated that cost was the main limitation for use of biologic products. This further supported the increased frequency of use for PRP over MSCs by the surveyed population. Future experimental trials could focus on comparing the efficacy of MSCs and PRP in multiple musculoskeletal conditions. Additional studies could justify the extra cost of MSCs if MSCs show improved healing over PRP.

Autologous conditioned serum and APS were most commonly administered intra-articularly. Autologous conditioned serum was the second most commonly used modality overall. In a 2007 study, ACS reduced lameness in an experimental model of osteoarthritis.[11] While APS is a relatively new commercially marketed technology with limited experimental and clinical studies,[13,21] 46% of respondents affirmed use of APS at least once per year. Like ACS, APS has also proven to be effective in reducing lameness in horses with previously diagnosed osteoarthritis of high-motion joints.[13] The survey indicated that APS is a more convenient therapy than ACS; 19% of respondents indicated inconvenience as a barrier to use of ACS in comparison with 2% for APS. Eight percent of respondents also indicated limited access to equipment as a limitation to the use for APS. If convenience is a factor in the selection of biologic therapies for musculoskeletal conditions, the authors expect to see a continued increase in the use of APS for intra-articular applications.

Some scientific studies or review publications have suggested dosing intervals for PRP,[22,23] ACS,[11] or MSCs.[24] However, no consensus currently exists regarding the timing of the first injection of biologic products or optimal treatment intervals and manufacturers do not include detailed instructions regarding the timing of initial or repeated injections. Our study indicated a large disparity in current treatment intervals for all biologic therapies. For example, PRP was most frequently repeated 1-2 months after the initial injection (38%) but 33% of respondents treated sooner (2-4 weeks following the initial injection) and 22% of respondents repeated treatments later than 2 months. Most respondents did not repeat administration of APS, consistent with the initial studies, which did not suggest a need for a scheduled redosing.[13] If APS was repeated, it was most commonly repeated >4 months postinjection. This long dosing interval could have indicated a return of lameness. However, the clinical indications for repeating injections were not addressed in this survey, and the reasoning for repeated injections is outside of the scope of this study.

Limited studies have reported adverse effects of biologic therapies,[21,25] and smaller, retrospective, or controlled studies may have underestimated the adverse effects experienced in clinical practice. That stated, the results from our study cannot easily be compared with retrospective or prospective studies with a finite case population. Our study described only the percentage of respondents who have experienced adverse effects associated with the use of biologic therapies, irrespective of the number of times the respondent has used that therapy. Answers were also based on subjective recall not clinical records. Local inflammation was reported more commonly with MSCs (83%) and PRP (86%) than with ACS (65%), and APS (55%). A survey performed by Velloso et al. in 2020 displayed similar findings but reported an overall lower incidence of joint flare.[16] This was expected, as our survey allowed for signs of local inflammation associated with both intrasynovial and intralesional administration whereas Velloso et al. (2020) reported joint flare only. Infection at the site of injection was the second most common adverse effect reported for all biologic therapies. This was surprising, as recent studies have indicated a low rate of infection as a result of biologic therapy use.[26–28] Although it is difficult to compare to experimental studies for reasons already elucidated, MSC were most frequently associated with infection at the injection site in comparison with other biologic therapies. Our study indicates that the risk of both local inflammation and infection should be recognized by practitioners that utilize biologic therapies and communicated to owners as a potential risk of treatment. Further large, retrospective studies are warranted to investigate this risk in all biologic therapies, especially MSC.

This study has several important limitations. The electronic survey was only sent to diplomates of the ACVS and ACVSMR. The results may not therefore reflect use by individuals in other specialties or by non-specialists. By surveying only board-certified specialists, this may have selected for a population of veterinarians with greater access to hospital conditions appropriate for MSCs or ACS processing. The authors also recognize the possibility of response bias because individuals who use biologic therapies may have been more compelled to answer this survey. The response rate for this study was 36%, which indicates that this survey reflects a minority of the population contacted. Combined with the possibility of response bias, this study may not reflect the true prevalence of the use of biologic therapies in equine practice. Further, compressing groups for analysis (years in practice, practice type) may have led to additional assessment bias. Not all participants provided answers for all questions, resulting in some participation bias. However, investigators were careful to inform participants that they need not use biologic therapies to complete the survey. Despite these limitations, this study provided detailed insight into the clinical use of biologics therapies for equine musculoskeletal disease and is the first to assess the use of these therapies by large animal specialists. The study provided important information on the current use, treatment protocols, negative effects, and limitations of use of these products for a variety of musculoskeletal conditions.

Biologic therapies are being broadly used by large animal specialists. Due to the current paucity of available information regarding these therapies, the information collected by this survey provides a baseline

understanding of common practices and helps to support the continued use and investigation of these products. Larger clinical trials are warranted to determine treatment efficacy, optimal treatment intervals, and to compare these available therapies for a variety of musculoskeletal conditions.

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**Author Contributions:** Colbath AC, VMD, PhD, DACVS: Involved in designing the survey, administering the survey, completing the data analysis, and preparation of the manuscript. Knott LE, DVM: Involved in designing the survey, administering the survey, completing the data analysis, and preparation of the manuscript. McIlwraith CW, BVSc, PhD, DSc, FRCVS, DACVS, DACVSMR: Involved in designing the survey, administering the survey, completing the data analysis, and preparation of the manuscript. Goodrich LR, DVM, PhD, DACVS: Involved in designing the survey, administering the survey, completing the data analysis, and preparation of the manuscript. O'Connor A, BVSc, MVSc, DVSc, FANZCVSc: Aided in data analysis and manuscript preparation. Fonseca-Martinez BA, DVM, MSc: Aided in data analysis and manuscript preparation.

## CONFLICT OF INTEREST

Dr. Laurie Goodrich is a shareholder in Advanced Regenerative Therapies (Fort Collins, Colorado) and a member of the scientific advisory board for EQCell, Inc. (Guelph, Canada). Dr. Wayne McIlwraith is a shareholder in Advanced Regenerative Therapies (Fort Collins, Colorado), a member of the board of directors of EQCell Inc. (Guelph, Canada), and a consultant for Arthrex (Naples, Florida). The remaining authors declare no conflict of interest related to this report.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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