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REVIEW ARTICLE

Evidence of the clinical effect of commonly used intra-articular treatments of equine osteoarthritis

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Summary

Background: Osteoarthritis (OA) is a common disease in equine patients that causes joint pain and loss of function. The aetiology of OA is assumed to be multifactorial. A range of medical treatments are on the market for symptomatic treatment of OA in equine patients, both biological and conventional options. Today, no true disease-modifying osteoarthritis drug (DMOAD) is available.

Objective: To summarise the current evidence of the clinical effect of commonly used intra-articular treatments of equine OA, specifically the use of intra-articular glucocorticosteroids (IA-GCs), intra-articular hyaluronic acid (IA-HA), intra-articular platelet-rich plasma/autologous-conditioned plasma (IA-PRP), intra-articular interleukin-1 receptor antagonist protein/autologous-conditioned serum (IA-IRAP) and intra-articular mesenchymal stem cells (IA-MSCs).

Study design: Systematic review.

Methods: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, a comprehensive search identified 22 clinical studies where horses with OA, naturally occurring or induced, were treated with one of the mentioned intra-articular treatments. The studies were reviewed to collect all in vivo studies with clinical follow-up on horses with OA.

Results: IA-GCs seem to have a beneficial short-term clinical outcome. Treatment with IA-HA shows varying clinical results and provides uncertain evidence for a beneficial clinical effect. IA-PRP shows overall promising clinical results for a significant improvement. IA-IRAP shows promising significant clinical effect, but most of the studies lack a control group for comparison. IA-MSCs show varying clinical results, but a majority of the included studies show evidence for a significant improvement in clinical effect.

Conclusion: To provide stronger evidence of the clinical effect of the five chosen treatments, further blinded, randomised and placebo-controlled studies are needed.

KEYWORDS
horse, intra-articular, lameness, osteoarthritis, treatment

INTRODUCTION

Osteoarthritis (OA) is a common disease in equine patients, causing up to 60% of all lameness cases (McIlwraith et al., 2012). The progression of OA is characterised by pathological changes in the joint environment such as calcification and degeneration of articular cartilage, osteophyte formation, synovitis and sclerosis of the subchondral bone. In addition, ligaments, periarticular tissue and the joint capsule are affected, all of which contribute to joint dysfunction and pain (McIlwraith, 2016; Ratneswaran et al., 2020).

The aetiology of OA in horses is assumed to be multifactorial, with three main hypothesised pathogenetic mechanisms: defective cartilage with abnormal biomechanical properties, physical changes in the subchondral bone and post-traumatic secondary to mechanical forces. Of those three pathways, the main aetiology of OA in horses is assumed to be post-traumatic (Caron, 2011). In current equine practice, the diagnosis of OA is commonly based on clinical signs, such as lameness, joint effusion and synovial fluid parameters, combined with radiographic evaluation. The accessibility of more sensitive imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), nuclear scintigraphy and ultrasonography is still increasing and can potentially be an effective supplement for detecting earlier stages of OA (Caron, 2011).

Osteoarthritis is a common joint disease in humans, as it is estimated that 240 million people worldwide suffer from the disease (Baker et al., 2022). OA in human patients causes similar symptoms as in the equine patients—pain and reduction in range of motion (ROM) of the affected joint (Taruc-Uy & Lynch, 2013). Over the last decade, interest, and use of intra-articular orthobiologic treatments, including platelet-rich plasma and mesenchymal stem cells, has gained increasing popularity in clinical practice. Reasons for this increased popularity include the potential to prevent OA progression, reduction in symptoms and improvement of joint function while reducing the potential of severe adverse events (Zaffagnini et al., 2022).

Today, multiple treatments are on the market to reduce symptoms of OA for equine patients such as biological cell-based therapies as well as conventional treatment options like intra-articular glucocorticosteroids or hyaluronic acid, used separately or in combination (Contino, 2018). Glucocorticosteroids, hyaluronic acid and biologics seem to be the most commonly used intra-articular treatments for OA and synovitis in horses. Limited treatment options are available having the potential of reversing OA progression, and no true disease modifying osteoarthritis drug (DMOAD) is on the market. Secondary to the wide variety of treatment options for OA, multiple factors affect the drug of choice with the experience and preferences of the veterinarian being one of the strongest factors (Ferris et al., 2011; Knott et al., 2022).

Glucocorticosteroids are a pharmacological treatment that inhibit the inflammatory process at all stages (McIlwraith, 2010). Hyaluronic acid is a natural polymer, that belongs to the group of glycosaminoglycans, which is one of the main components in the extracellular matrix of the hyaline cartilage. Hyaluronic acid is produced by most cell types and therefore have multiple biological functions. In the joint, hyaluronic acid provides viscoelastic characteristics to the synovial fluid (Marinho et al., 2021). Platelet-rich plasma/autologous conditioned plasma is an autologous blood product. It contains a great quantity of platelets within a small amount of plasma, but a variable concentration of platelets between individuals due to biological variation. Autologous blood products utilise mechanisms of the natural response to injury, for example production of anti-inflammatory cytokines and release of growth factors (Brossi et al., 2015). Another autologous blood product is interleukin-1 receptor antagonist protein/autologous conditioned serum which increases the production of different anti-inflammatory cytokines, including interleukin-1 receptor antagonist (IL-1Ra). IL-1Ra has been claimed to be one of the key proinflammatory mediators involved in OA (Tokawa et al., 2022). Mesenchymal stem cells are stromal cells, that in horses can be isolated from a wide spectrum of tissues—for example bone marrow, dental pulp, umbilical cord and muscle tissue. Mesenchymal stem cells have the capacity to self-renew, to manifest multilineage differentiation as well as immunomodulatory effects (Gugjoo et al., 2019).

The aim of this study is to conduct a systematic review on the current evidence of the clinical effect of commonly used intra-articular treatments of equine OA, specifically the use of intra-articular glucocorticosteriods (IA-GCs), intra-articular hyaluronic acid (IA-HA), intra-articular platelet-rich plasma/autologous-conditioned plasma (IA-PRP), intra-articular interleukin-1 receptor antagonist protein/autologous-conditioned serum (IA-IRAP) and intra-articular mesenchymal stem cells (IA-MSCs). Several possible treatments are available on the market for treatment of equine osteoarthritis. However, it is not within the scope of the review to cover all possible treatment options. The focus of this review was biological therapies with the potential of slowing down/reversing the disease progression and compare these to hyaluronic acid and glucocorticosteroids since these are the oldest and most commonly used joint treatments in horses.

MATERIALS AND METHODS

Search strategy

This systematic review was conducted using the guidelines from the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Page et al., 2021). From 21 March to 24 March 2023, the following four online search platforms were used: PubMed, Embase, Web of Science and Scopus, to identify and collect relevant literature. The literature search was made separately for the five different treatments (IA-GCs, IA-HA, IA-PRP, IA-IRAP and IA-MSCs), using the same search strategy: (horse* OR equine) AND (osteoarthritis OR OA OR arthrosis) AND (treatment*) AND (intra-articular OR intra-articular OR intra articular) AND (keywords for one of the five listed treatment groups), as shown in Table S1. Systematic literature

search—search terms. All selection and elimination of studies were made by all authors. No restrictions were applied considering publication date.

Inclusion criteria

Studies included in this systematic review consisted of experimental studies conducted on horses with OA, naturally occurring or induced, in the limbs. Included horses should have undergone intra-articular treatment with either, GCs, HA, PRP/ACP, IRAP/ACS or MSCs. Only in vivo studies where the clinical effect was investigated were included.

Exclusion criteria

Studies were excluded if the horses did not suffer from OA. Studies were excluded if the treated animals were animals other than horses and if the treatment method was not intra-articular. All in vitro studies and studies without follow-up were excluded. All studies on horses with OA, treated in other regions than the limbs, were excluded. Studies written in languages other than English, Danish or Swedish were excluded.

Risk of bias

Included studies were analysed to assess the potential risk of bias. The following 7 bias characteristics were used: random sequence generation (selection bias), allocation bias (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias) (Higgins et al., 2011). The bias characteristics are classified as 'low' (green), 'unclear' (yellow) or 'high risk' (red). The overall judgement is defined as 'low risk' when all domains are considered low risk of bias and as 'unclear' if all domains are considered low or unclear risk of bias. If at least one domain or more are classified as 'high risk of bias' the overall judgement is 'high risk of bias'. Retrospective studies were not graded.

RESULTS

By the initial literature search, a total of 596 studies were identified. After manual removal of duplicates, screening of titles and abstracts, and assessment for eligibility, 22 studies remained and were included in this systematic review, as presented in the PRISMA flow chart (Figure 1).

Eighteen of 22 included studies were analysed to assess the risk of bias (Figure 2), retrospective studies were not graded. Overall, <12% of the included studies were assessed as overall low risk of bias (Figure 3).

Intra-articular glucocorticosteriods (IA-GCs)

The latest completed study (de Clifford et al., 2021) investigated treatment with triamcinolone acetonide (TA) on naturally occurring OA in the middle carpal joint and found that 27.3% of the horses treated with TA were free from lameness 6-week post-treatment. 9.1% of the TA-treated horses had success, defined as complete resolution in reaction to carpal flexion of the joint and 0% had success in the joint effusion parameter (de Clifford et al., 2021).

De Grauw et al. (2016) investigated treatment with TA in different joints with naturally occurring OA and found that 87.8% of the horses had an improvement ≥2 degrees reduction in lameness score 3-week post-treatment. Lameness score and joint effusion scores improved significantly ($p < 0.0001$) 3 weeks after treatment compared with baseline. A follow-up 3-month post-treatment performed by a telephone questionnaire, assessed that 51.4% in the TA-treated group returned to their previous performance level, the level before they become lame (de Grauw et al., 2016).

A retrospective study (Labens et al., 2007) investigated methylprednisolone acetate (MPA) and TA with or without hyaluronic acid (HA) for the treatment of naturally occurring OA in the distal tarsal joint. They found that horses treated with either MPA or TA with or without HA improved after a median of 56 days ($p < 0.0001$), and there was no significant difference between the two GCs-preparations. 57.6% of the treated hindlimbs had an improved lameness score and 25.4% of them were free from lameness at the first re-examination, but 90.2% of the horses studied remained lame at the second examination. Horses treated once had a significant improvement ($p < 0.001$), while horses treated twice did not show a further significant improvement ($p = 0.141$) (Labens et al., 2007).

A retrospective study (Smith et al., 2005) also investigated corticosteroids either with or without sodium hyaluronan for the treatment of naturally occurring OA in the talocalcaneal or tarsocrural joint. They found no significant improvement in any horse and concluded that treatment with intra-articular corticosteroids appeared to have no clinical effect (Smith et al., 2005).

Overall, the studies indicate a good short-term clinical effect of treatment with IA-GCs. It does not seem to have an advantaged outcome when using GCs in combination with HA.

Intra-articular hyaluronic acid (IA-HA)

The most recent study (de Clifford et al., 2021) investigated treatment of naturally occurring OA in the middle carpal joint with sodium hyaluronate (SH) and found that 40% of the horses were free from lameness 6-week post-treatment. 20% of the SH-treated horses had success, defined as complete resolution in reaction to carpal flexion of the joint and 0% had success in the joint effusion parameter (de Clifford et al., 2021).

Niemelä et al. (2016) investigated treatment of naturally occurring OA in the metacarpophalangeal joint with nonanimal stabilised hyaluronic acid (NASHA) and found no significant improvement in

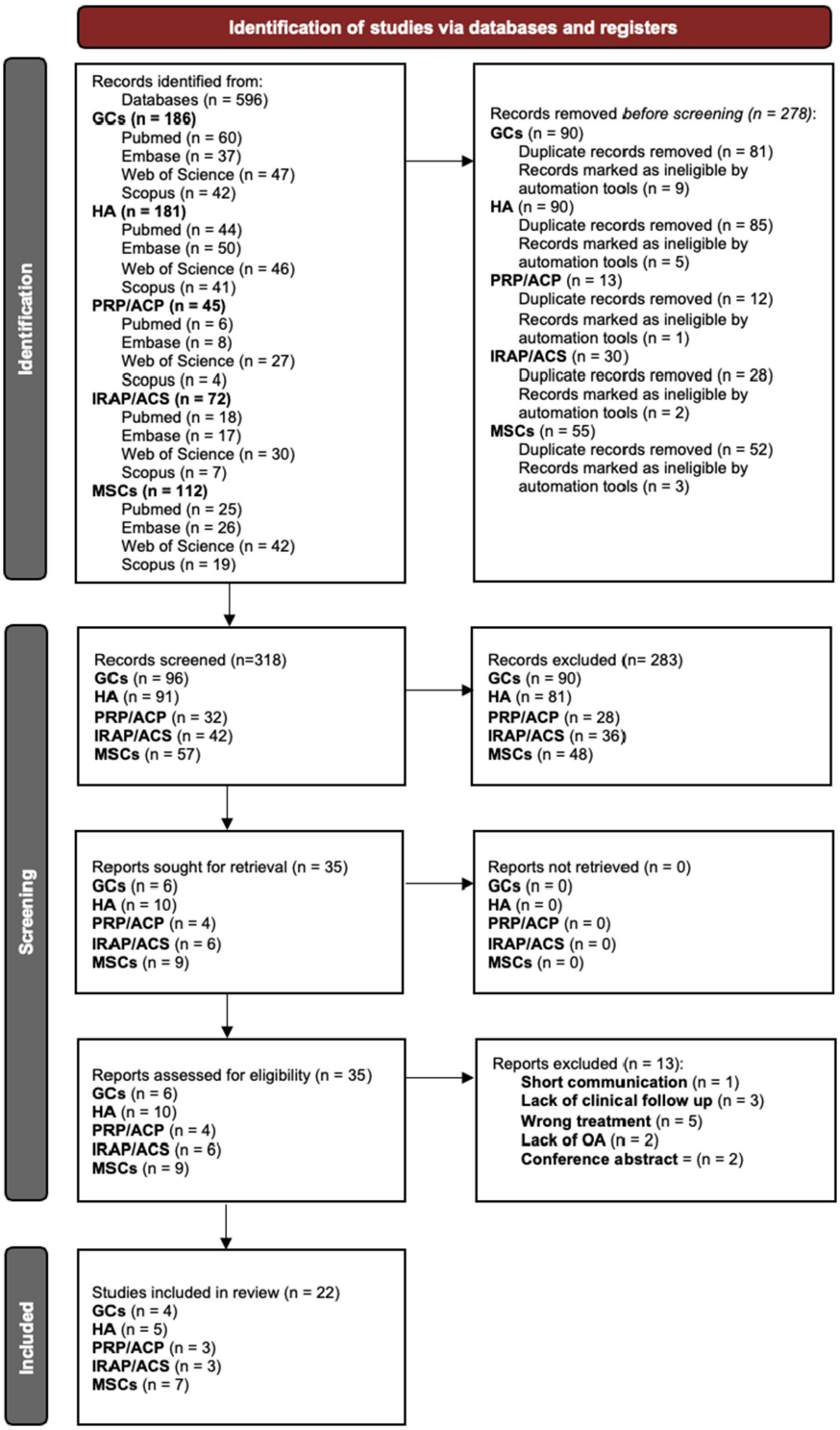

FIGURE 1 Flow chart following the PRISMA guidelines (Page et al., 2021). GCs, glucocorticosteroids; HA, hyaluronic acid; IRAP/ACP, interleukin-1 receptor antagonist protein/autologous conditioned serum; MSCs, mesenchymal stem cells; OA, osteoarthritis; PRP/ACP, platelet-rich plasma/autologous conditioned plasma.

lameness score ($p = 0.94$) compared with the placebo group. A significant improvement was recorded in the flexion test ($p = 0.01$) compared with the placebo group, while joint effusion and pain in the flexion test were similar between the NASHA and placebo-treated group. A follow-up by a telephone interview 3-month post-treatment showed that 67% of the horses returned to their previous exercise level (Niemelä et al., 2016). However, the results do not consider that only half of the horses had mild findings on radiographs whereas the other half suffered from synovitis only (i.e. had no detectable abnormalities on radiography).

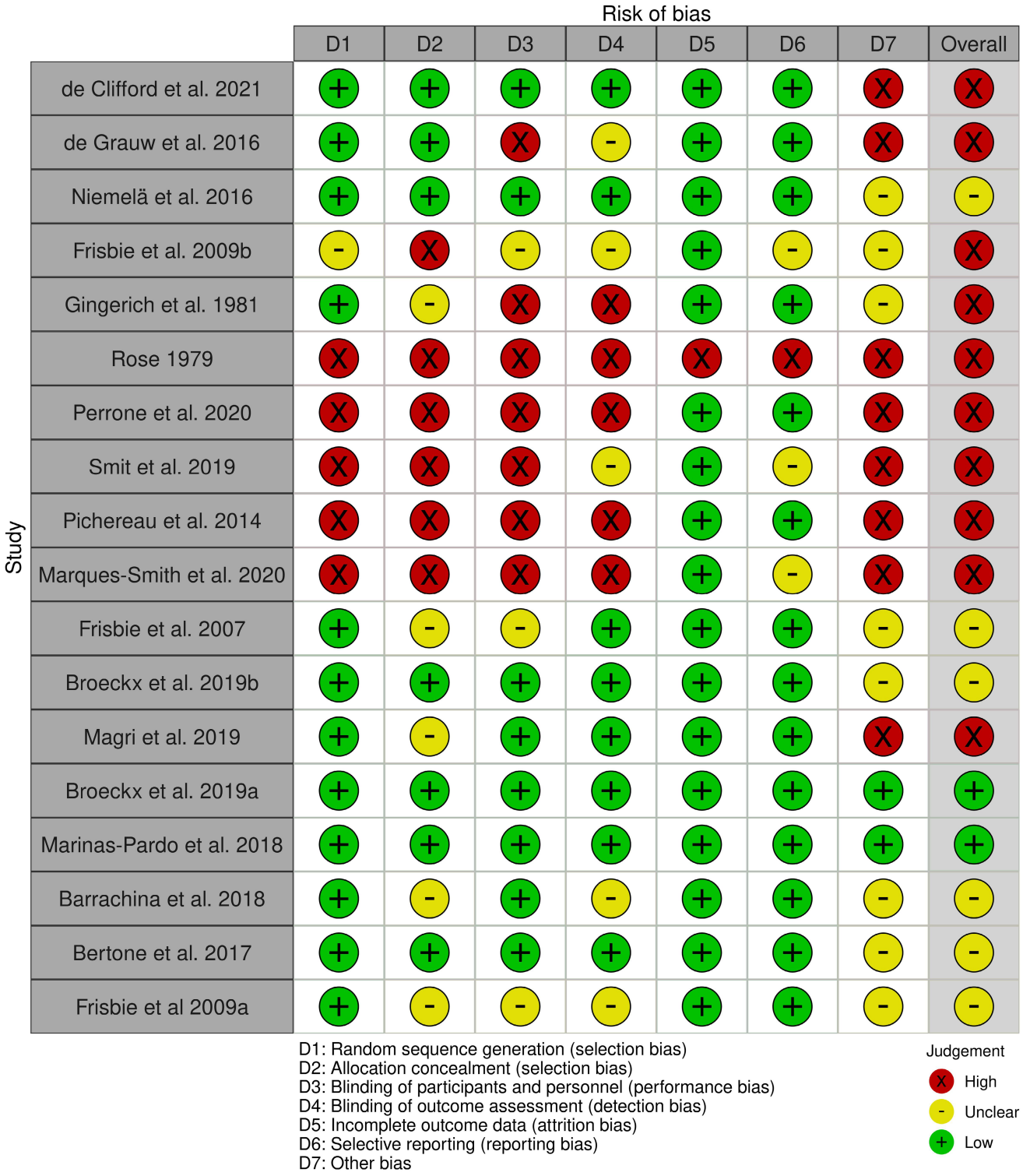

FIGURE 2 Summary of risk of bias (McGuinness & Higgins, 2020).

Frisbie, Kawcak, et al. (2009) treated experimentally induced OA in the middle carpal joint with SH and did not find a significant improvement in the lameness score due to treatment. No significant effects in carpal flexion or joint effusion were observed due to treatment compared with the control group (Frisbie, Kawcak, et al., 2009).

A randomised placebo-controlled study (Gingerich et al., 1981) investigated treatment with different doses of hyaluronic acid (HA) for the treatment of experimentally induced OA in the intercarpal joint. They found that low dosages (0, 5 or 10 mg) did not have any significant changes in lameness score and joint function 4-week post-treatment, while high dosages (20 and 40 mg) showed clinical improvement in lameness and joint function with only one horse not completely free from lameness 1-week post-treatment (Gingerich et al., 1981). Force plate data showed that peak vertical

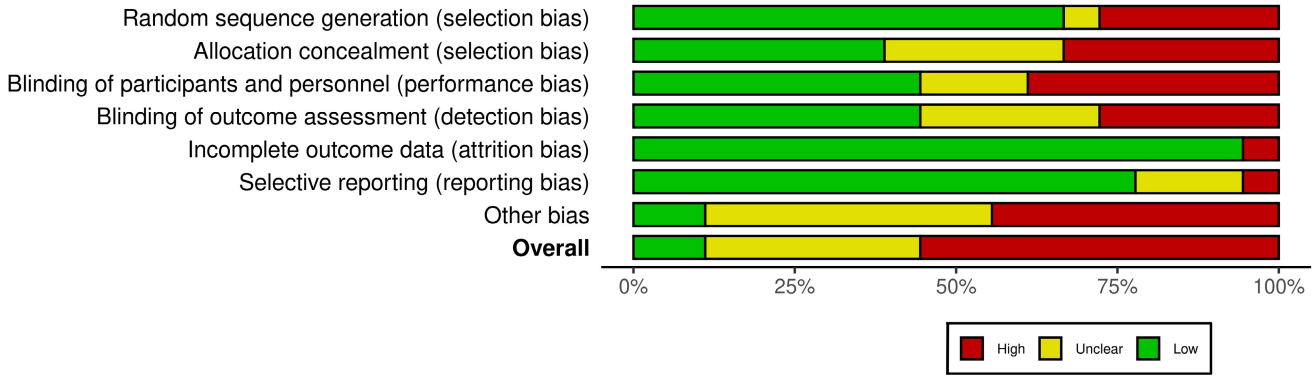

FIGURE 3 Risk of bias shown in percentage (McGuinness & Higgins, 2020).

forces (percent Fmax) were equally shared between forelimbs and hindlimbs before arthritis induction, while afterwards the weight redistributed to decrease the maximal vertical force on the lame limb. In horses treated with low dosages IA-HA Fmax remained abnormally distributed throughout the study period, while horses treated with high dosages IA-HA had returned to normal within 1-week post-treatment and remained normal throughout the study period (Gingerich et al., 1981).

Another study (Rose, 1979) also investigated treatment with SH on naturally occurring OA and found that the effect of treatment was variable in duration. Initially, all horses showed a great response with lameness disappearing. Some horses were still free from lameness 3–12 months post-treatment while other horses' lameness returned. The study also reports that some horses showed improvement in the range of joint flexion (Rose, 1979).

Overall, the studies show very variable and inconsistent evidence for a clinical effect of IA-HA.

Intra-articular platelet-rich plasma/autologous conditioned plasma (IA-PRP)

The newest completed study (Perrone et al., 2020) investigated the use of autologous platelet-rich plasma on naturally occurring OA in the intertarsal joint and found that the lameness score was significantly improved ($p < 0.01$) at a follow-up after 60 days compared with baseline. The study confirmed a beneficial clinical effect for a period of 60 days, the improvement was seen as a decrease of lameness, decrease in synovial effusion and a decrease in pain at forced flexion (Perrone et al., 2020).

Smit et al. (2019) investigated treatment with platelet-rich plasma on naturally occurring OA. The study found no significant clinical improvement after a follow-up 56-day post-treatment on joint flexion score, synovial effusion score and periarticular signs. The study did not show their results on the lameness evaluation performed during the study period due to unforeseen external factors which influenced the results (Smit et al., 2019).

Pichereau et al. (2014) found that lameness scores were significantly improved ($p < 0.0001$) after treatment with autologous platelet concentrate on naturally occurring OA. Significant improvement ($p = 0.0001$) in terms of physical function, stiffness and joint pain were assessed by the owners using a modified index survey, while the lameness evaluation was performed by a clinician. The study (Pichereau et al., 2014) had no control group for comparison, but did follow-up 1-year post-treatment, and found that 80% of treated horses were able to resume work at the same competition level.

Overall, the studies indicate a promising clinical effect of IA-PRP, but it is difficult to give an evidence-based recommendation based on three studies where none of them is categorised as high level of evidence.

Intra-articular interleukin-1 receptor antagonist protein/autologous conditioned serum (IA-IRAP)

The latest completed study (Bertuglia et al., 2021) investigated treatment with interleukin-1 receptor antagonist protein on naturally occurring OA in the fetlock joint. They found that lameness score and digital flexion test response significantly improved ($p < 0.05$) after 6-month follow-up compared to baseline. The study did not have a control group for comparison (Bertuglia et al., 2021).

Marques-Smith et al. (2020) investigated treatment with autologous conditioned serum (ACS) and found that 11 out of 19 horses responded to treatment and were free from lameness at re-evaluation 2 weeks after the third injection. It is worth mentioning that the horses in this study were treated in different joints, had various radiographic findings and there was no control group for comparison (Marques-Smith et al., 2020).

Frisbie et al. (2007) investigated treatment of experimentally induced OA in the middle carpal joint with ACS and found that lameness scores significantly improved ($p = 0.001$) 70-day post-treatment compared with the placebo-treated group. Joint effusion, response to flexion and joint manipulation did not show any significant improvement in response to treatment (Frisbie et al., 2007).

Overall, the studies indicate a good clinical effect, but none of the three included studies were categorised as high level of evidence, which makes the results uncertain.

Intra-articular mesenchymal stem cells (IA-MSCs)

The most recent completed study (Broeckx, Martens, et al., 2019) investigated treatment of experimentally induced OA in the metacarpophalangeal joint with an investigational veterinary product consisting of peripheral blood-derived equine allogenic chondrogenic induced mesenchymal stem cells combined with equine allogenic plasma. They found that joint effusion significantly decreased ($p=0.01$) 11-week post-treatment, lameness scores ($p=0.002$) and response to flexion test ($p=0.001$) significantly improved after Week 7 and onwards, all compared with the control group. No significant differences in joint circumference were observed during the study (Broeckx, Martens, et al., 2019). Objective lameness evaluation showed that the vector sums, which is a measure of amplitude of forelimb lameness, on the treadmill ($p=0.02$) and on a straight line after flexion ($p=0.05$) were significantly lower in the MSCs-treated group compared with the control group. On a straight line before flexion and on the left circle the vector sums were lower compared with the control group, but not significantly. The pressure plate analysis did not find any significant differences in symmetry indices between the groups (Broeckx, Martens, et al., 2019).

A study (Magri et al., 2019) investigated treatment of naturally occurring OA in the metacarpophalangeal joint with allogenic, umbilical cord-derived, neonatal mesenchymal stem cells. They found that lameness scores ($p<0.0017$), joint distension ($p=0.021$), passive flexion ($p=0.001$) and active flexion scores ($p=0.001$) significantly improved at follow-up 6 months post-treatment compared with baseline. The study compared the effect of treatment with either one or two MSC injections and found that apparently there was no clinical benefit of repeated administration (Magri et al., 2019).

Another study (Broeckx, Seys, et al., 2019) also found improvement in lameness scores after treatment with an investigational veterinary product consisting of peripheral blood-derived equine allogenic chondrogenic induced mesenchymal stem cells combined with equine allogenic plasma. Broeckx, Seys, et al. (2019) investigated treatment of naturally occurring OA in the fetlock joint and found that lameness scores ($p<0.001$), response to flexion test ($p<0.001$) and joint effusion scores ($p<0.001$) significantly improved 18 weeks after treatment compared with the placebo-treated group. A long-term follow-up was performed one-year post-treatment and found that significantly ($p<0.001$) more MSCs-treated horses returned to their previous training level or were working at training level compared with the placebo-treated horses (Broeckx, Seys, et al., 2019).

Marinas-Pardo et al. (2018) investigated treatment of naturally occurring OA with allogenic adipose derived mesenchymal stem cells. At 90-day follow-up, they found significant reduction in lameness ($p<0.05$) compared with a control group. 26 of the 37 MSCs-treated horses responded to treatment, 18 of those horses were responders on Day 45 after one injection while eight horses received a second injection resulting in improved lameness score on Day 90 (Marinas-Pardo et al., 2018).

Barrachina et al. (2018) compared treatment with either naive allogenic mesenchymal stem cells or proinflammatory primed allogenic mesenchymal stem cells with a control group. They did not find a significant difference in lameness scores and local heat between the groups, but the results suggested a faster reduction in lameness and local heat in the two groups treated with MSCs. Carpal perimeter significantly improved ($p<0.05$) in the MSCs-primed group compared with both the MSCs-naïve-treated horses and the control group (Barrachina et al., 2018).

Bertone et al. (2017) investigated treatment with equine dental pulp connective tissue particles in different joints with naturally occurring OA. The lameness scores improved within the OA horses but were not statistically significant ($p<0.07$). The limb circumference did not improve significantly between the groups compared with baseline, but there was a significant effect over time ($p<0.04$). Pain score to flexion test and average goniometric measurement for pain-free range of motion did not show any significant improvement compared with the other groups or time (Bertone et al., 2017). Kinetic gait analysis was performed and showed no significant differences in velocity, but asymmetry index (AI) for vertical force peak (VFP) and coefficients of variation (CV) for VFP decreased significantly compared with baseline ($p<0.05$) for MSCs-treated horses, especially the OA horses. AI for vertical force impulse (VFI) for horses in the OA group ($p<0.04$) and CV-VFI (The study states CV-VPI in their results, but this abbreviation is not explained in the article. Based on our review of the results, we believe that it is supposed to be CV-VFI.) ($p<0.03$) was significantly lower in the MSCs-treated group compared with baseline, both corresponding to less lameness (Bertone et al., 2017).

Experimentally induced osteoarthritis in the middle carpal joint was treated with either adipose derived stromal vascular fraction (ADSVF), bone marrow-derived mesenchymal stem cells (BMDMSC) or placebo (Frisbie, Kisiday, et al., 2009). The results indicated no significant improvement in lameness scores and joint effusion 70 days post-treatment in any comparison. A significant improvement in the placebo group and the BMDMSC-treated group was seen in flexion score ($p=0.0013$) compared with the ADSVF-treated group (Frisbie, Kisiday, et al., 2009).

Overall, the studies indicate a promising clinical effect of IA-MSCs, as most studies were both randomised, blinded and placebo-controlled.

All the included studies are summarised in Table 1.

DISCUSSION

Overall, the reviewed studies of IA-GCs suggest a beneficial short-term effect, but no study had a control group for comparison, and none of the studies were both randomised and blinded. IA-GCs in combination with IA-HA does not seem to have an improved clinical outcome compared with IA-GCs alone. The result for IA-HA showed varying clinical results and provides uncertain evidence for a beneficial clinical effect. Treatment with IA-PRP showed overall promising improvement in clinical effect, but none of the included studies were randomised, blinded and placebo-controlled. Reviewed studies showed a promising clinical

TABLE 1 Summary of the studies included in this systematic review.

Reference	Study design	Number of horses	Treatment	Control group	Follow-up	Clinical effect (Significant changes)
Glucocorticosteriods						
de Clifford et al. (2021)	Prospective double-blinded positive control study	31 (39 joints)	Triamcinolone acetonide ($n=11$) (14 joints)	No	6 weeks ($n=9$) (11 joints)	–
de Grauw et al. (2016)	Prospective, randomised, parallel, open-label, multicentre clinical trial	80	Triamcinolone compared with triamcinolone with hyaluronate	No	3 weeks ($n=80$)	Lameness score and joint effusion significantly improved
Labens et al. (2007)	Retrospective study	51 (59 hindlimbs)	Methylprednisolone acetate (MPA) or triamcinolone acetonide (TR), either with or without hyaluronic acid (HA) MPA, $n=38$ hindlimbs TR, $n=4$ hindlimbs TR + HA, $n=17$ hindlimbs	No	18–1436 days	Lameness score significantly improved
Smith et al. (2005)	Retrospective study	18	Corticosteroids (± sodium hyaluronan) ($n=8$)	No	–	No significant clinical improvement
Hyaluronic acid						
de Clifford et al. (2021)	Prospective double-blinded positive control study	31 (39 joints)	Sodium hyaluronate ($n=10$) (12 joints)	No	6 weeks ($n=8$) (10 joints)	–
Niemelä et al. (2016)	Randomised, double-blinded, placebo-controlled clinical study	27	Nonanimal stabilised hyaluronic acid ($n=14$) (7 with mild findings in x-rays)	Yes ($n=13$) (7 with mild findings in x-rays)	2 weeks (2.5–3 months)	Flexion test score significantly improved
Frisbie, Kawcak, et al. (2009)	Blinded and placebo-controlled study	24	Sodium hyaluronate ($n=8$)	Yes ($n=8$)	70 days	No significant clinical improvement
Gingerich et al. (1981)	Randomised and placebo-controlled study	25	Hyaluronic acid (0, 5, 10, 20 or 40 mg)	Yes ($n=5$)	4 weeks	Lameness score significantly improved
Rose (1979)	Longitudinal study	16	Sodium hyaluronate	No	3–12 months	–
Platelet rich plasma/Autologous conditioned plasma						
Perrone et al. (2020)	Longitudinal study	44	Autologous platelet-rich plasma	Yes[a] ($n=21$)	60 days	Lameness score significantly improved
Smit et al. (2019)	Longitudinal study	10	Platelet-rich plasma	Yes ($n=5$)	56 days	No significant clinical improvement
Pichereau et al. (2014)	Longitudinal study	20	Autologous platelet concentrate	No	1 year	Lameness score significantly improved

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number of horses	Treatment	Control group	Follow-up	Clinical effect (Significant changes)
Interleukin-1 receptor antagonist protein/Autologous conditioned serum						
Bertuglia et al. (2021)	Retrospective observational study	100	Interleukin-1 receptor antagonist protein ($n=25$)	No	6 months	Lameness score and digital flexion test response significantly improved
Marques-Smith et al. (2020)	Single-centre prospective cohort study	20	Autologous conditioned serum	No	2 weeks after the third injection ($n=19$)	11 out of 19 horses respond to treatment[b]
Frisbie et al. (2007)	Randomised, placebo-controlled study	16	Autologous conditioned serum	Yes ($n=8$)	70 days	Lameness score significantly improved
Mesenchymal stem cells						
Broeckx et al. (2019b)	Randomised, double-blinded, placebo-controlled experiment	12	Equine allogenic chondrogenic-induced mesenchymal stem cells with equine allogenic plasma ($n=6$)	Yes ($n=6$)	11 weeks ($n=12$)	Lameness score, response to flexion test and joint effusion significantly improved
Magri et al. (2019)	Multicentre, randomised, double-blinded, controlled, clinical pilot study	28	Allogenic, umbilical cord-derived, neonatal mesenchymal stem cells 1 injection ($n=14$) 2 injections ($n=14$)	No	6 months ($n=22$) 1 injection ($n=10$) 2 injections ($n=12$)	Lameness score, joint distension, passive flexion, and active flexion scores significantly improved
Broeckx, Seys, et al. (2019)	Randomised, multicentre, double-blinded, and placebo-controlled study	75	Equine allogenic chondrogenic-induced mesenchymal stem cells with equine allogenic plasma ($n=50$)	Yes ($n=25$)	18 weeks ($n=73$)	Lameness score, response to flexion test and joint effusion significantly improved
Marinas-Pardo et al. (2018)	Parallel-group, blind, randomised and controlled (placebo-control group) clinical trial	72	Allogenic adipose-derived mesenchymal stem cells ($n=39$)	Yes ($n=33$)	90 days ($n=70$)	Lameness score significantly improved
Barrachina et al. (2018)	Randomised, blinded and placebo-controlled study	18	Naive allogenic mesenchymal stem cells ($n=7$) Proinflammatory primed allogenic mesenchymal stem cells ($n=7$)	Yes ($n=4$)	6 months ($n=18$)	Carpal perimeter significantly improved in the mesenchymal stem cell-primed group
Bertone et al. (2017)	Prospective, randomised, blinded and controlled clinical trial	40 (20 with OA)	Equine dental pulp connective tissue particles	Yes ($n=20$) (10 with OA)	2 weeks ($n=40$) (20 with OA)	Asymmetry index and coefficients of variation for vertical force peak and vertical force impulse significantly improved

TABLE 1 (Continued)

Reference	Study design	Number of horses	Treatment	Control group	Follow-up	Clinical effect (Significant changes)
Frisbie et al. (2009a)	Randomised and placebo-controlled study	24	Adipose-derived stromal vascular fraction ($n=8$) Bone marrow-derived mesenchymal stem cells ($n=8$)	Yes ($n=8$)	70 days	Flexion score significantly improved in the bone marrow-derived mesenchymal stem cell-treated group

Note: The clinical effects column only summarises the significant changes.

[a] The control group consisted of synovial fluid samples from healthy horses without previous history of joint disease (Perrone et al., 2020).

[b] ACS content of IGF-1 and IL-1Ra was significantly associated with clinical response ($p=0.01$ and $p=0.03$, respectively) (Marques-Smith et al., 2020).

effect of IA-IRAP. However, only one study was randomised and had a control group for comparison, none of the studies were blinded. IA-MSCs showed overall positive clinical effect, and most studies were randomised, blinded and placebo-controlled. In general, many studies were only categorised as low-level evidence; not randomised, not blinded, no control group, short follow-up, no objective gait analysis etc. It is worth mentioning that none of the 22 included studies reported serious adverse side effects (Table S2: Adverse effects), but the long-term effect and safety are uncertain as most studies only had a short follow-up period.

The lack of blinding and randomisation may lead to high bias within the majority of the included studies. Randomised, blinded and placebo-controlled studies are designed to limit all potential observation and selection bias and therefore have a high level of evidence. It is important to limit bias to avoid erroneous conclusions in clinical research. The lack of a control group may be due to the ethical animal welfare perspective. However, it is important to realise that lack of control groups and other objective measures may lead to erroneous conclusions, hence potentially treatment of many patients with ineffective medications over a long period of time. Horses in the control group are at risk of suffering from joint related pain throughout the study period. A possible solution could be to treat the control group with a known golden standard, for example control groups in orthobiologic studies with GCs, and treatment with systemic NSAIDS in GCs studies. It can also be affected by the difficulty of finding a study population, that meets the chosen inclusion criteria. Private horse owners may also have concerns about whether their horse might end up in the control group and, as a consequence, not receive treatment.

Another important thing to consider is the time of follow-up. 6 of the 22 studies (Barrachina et al., 2018; Bertuglia et al., 2021; Labens et al., 2007; Magri et al., 2019; Pichereau et al., 2014; Rose, 1979) did a clinical follow-up at 6 months or longer post-treatment. It is therefore difficult to summarise the evidence of the treatment's long-term effect and safety. As mentioned, none of the five included treatments is a DMOAD but is used as symptomatic treatment of OA in horses. A long-term clinical follow-up is also important to provide evidence for the treating veterinarian about the effective duration of the treatment, and if and when to repeat treatment of the affected joint.

In 14 of the 22 studies, lameness evaluation was investigated using the American Association of Equine Practitioners (AAEP) grading system. The remaining eight studies used other scales to evaluate lameness (de Grauw et al., 2016; Frisbie et al., 2007; Gingerich et al., 1981; Magri et al., 2019; Perrone et al., 2020; Pichereau et al., 2014; Rose, 1979; Smith et al., 2005). Objective gait analysis was used in only four studies (Bertone et al., 2017; Broeckx, Martens, et al., 2019; Gingerich et al., 1981; Magri et al., 2019). One study (Magri et al., 2019) used objective gait analysis (Lameness Locator ND), but only during lameness evaluation in 6 out of 22 horses at the 6-month follow-up. The objective gait analysis agreed with the subjective evaluation (AAEP scale) in five out of six horses. Although most of the studies used the same subjective grading system for lameness evaluation (AAEP grading scale), it is important to take into consideration that subjective lameness investigation can be biased by the evaluating veterinarian, particularly

when used in a nonblinded study. It has been shown that subjective evaluation of lameness is not very reliable in horses with mild lameness (Keegan et al., 2010). In future studies, when using lameness as one of the clinical evaluation scores, objective gait analysis is more accurate and should be used as an indispensable method to the lameness evaluation. It is shown that Equinosis Q with Lameness Locator software selected the correct limb of lameness before the veterinarians in 58.33% ($p < 0.0001$) of the trials (McCracken et al., 2012). The conclusion is supported by Keegan et al. (2011) which suggests that an inertial sensor system is reliable to investigate lameness for clinical use.

It is also important to have in mind that the lack of standardisation of orthobiologics (PRP, IRAP and MSCs) makes it very difficult to ensure a uniform product. It is important to be aware that many different factors have an impact on the content of the orthobiologic products, including individual patient variation such as age, comorbidities and circumstances during harvest of cells/blood which may influence the cellular components in the product. A standardisation of these products is required to enable reproduction of studies and to allow complete comparison between studies, within the groups of orthobiologics. This is supported by a systematic review and meta-analysis (Mayet et al., 2023) analysing intra-articular administration of orthobiologics in horses with OA, which also points out the necessity of standardisation of the orthobiologics to be able to compare the long-term effects, and to determine the exact components to develop effective and standardised treatment protocols. Today, a wide range of different preparation protocols and formulas are used under the same terms. It is therefore important to be aware of this variation, when evaluating, choosing between, and using orthobiologics as a treatment of OA.

To provide stronger evidence of the clinical effect of the five chosen treatments, further blinded, randomised and placebo-controlled studies are needed.

Management of osteoarthritis in humans

A disease modifying osteoarthritis drug is currently not available in humane medicine. According to guidelines from Osteoarthritis Research Society International (OARSI) (Bannuru et al., 2019) and American College of Rheumatology (ACR) (Kolasinski et al., 2020), several different treatment modalities are recommended in the treatment of human OA. The guidelines facilitate that the course of treatment is made based on a mutual decision-making between clinician and the patient, so the treatment plan is organised and individualised.

The OARSI guidelines (Bannuru et al., 2019) also clarify intra-articular treatments. IA-GCs and IA-HA are conditionally recommended for treatment of knee OA. It is noted that IA-GCs may provide short-term pain relief, and IA-HA may have a beneficial effect at 12 weeks and beyond on pain relief. IA-HA seems to have a more favourable long-term safety profile, compared with repeated treatment with IA-GCs. IA-PRP and IA-MSCs are not recommended according to the guidelines due to extremely low quality of evidence and because the formulations currently are not standardised (Bannuru et al., 2019).

The American College of Rheumatology (ACR) and the Arthritis Foundation guidelines (Kolasinski et al., 2020), recommend IA-GCs for treatment of knee and/or hip OA and conditionally recommend it for treatment of hand OA. The guideline also addresses that a recent report, (McAlindon et al., 2017), draws attention to, that IA-GCs in a certain frequency or some specific steroid preparations, can contribute to cartilage loss. The ACR voting panel, however, was uncertain of the clinical significance since changes in cartilage thickness were not associated with aggravation in either pain, function or other radiographic chances (Kolasinski et al., 2020).

IA-HA is in general not recommended but can be used if any other treatment options fail to control the joint symptoms. The guidelines draw attention to benefits of IA-HA have been reported but restricted to studies with a high risk of bias. Trials with low risk of bias have in the meta-analysis shown that the effect of treatment approaches zero when compared to saline IA-injections (Kolasinski et al., 2020).

IA-MSCs and IA-PRP are strongly recommended against. This is due to concerns about heterogeneity and lack of standardisation, which makes it very difficult to identify what exactly is being injected. IA-IRAP is strongly recommended against, due to the known risks of toxicity and because efficacy has not been demonstrated (Kolasinski et al., 2020).

In general, Kolasinski et al. (2020) conditionally recommends IA-GCs over IA-HA and other IA-injections, due to higher quality evidence for efficacy than for the other treatment options.

Limitations

The literature search was conducted in four major databases; Scopus, PubMed, Web of Science and Embase, but no additional databases were searched, and no searches were made for grey literature. Therefore, there is a theoretical risk that additional relevant studies might have been missed. Second, only articles written in English, Danish or Swedish were included in the review, this might have excluded relevant studies written in other languages. However, only a small number of articles were excluded during the screening process due to this criterion. The main limitation of the study, and confusing aspect for equine clinicians, is the fact that PRP, IRAP and MSCs are not specifically defined drugs and differ between manufacturers, batches, clinicians and even individual horses. This makes it extremely difficult to compare and interpret the results between different studies.

CONCLUSION

The studies included in the present systematic review provides very variable, inconsistent and only low level of evidence of a lasting clinical effect of intra-articular treatments of horses with osteoarthritis.

There is currently no ideal disease modifying osteoarthritis drug on the market, but several symptom relieving medical preparations are available for treatment of equine osteoarthritis. It is the authors' interpretation that based on the included studies in this review, there seems to be some clinical effect of treatment with IA-MSCs in horses suffering from OA. However, there is a lack of clinical guidelines for the treatment of equine osteoarthritis which may be attributed to the lack of high-quality standardised clinical studies which are needed to ensure an effective, safe and certain treatment outcome. This makes the results very difficult to interpret and compare and therefore further randomised, blinded and placebo-controlled clinical trials are needed to provide more information about the efficacy of existing treatment options, and further research is needed to get closer to a true disease modifying osteoarthritis drug.

AUTHOR CONTRIBUTIONS

Anne Nedergaard: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization; writing – original draft. **Lisa Emilia Carlsson:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization; writing – original draft. **Casper Lindegaard:** Conceptualization; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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