Chapter 12
Platelet-Rich Plasma and Autologous Conditioned Serum: Non-Cellular Biologic Therapies for Neuroimmune Modulation and the Treatment of Arthritis Pain

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Abstract Osteoarthritis (OA) affects more than 50 million in the United States (Lawrence et al Part II Arthritis Rheum 58(1):26–35, 2008); however, most of these individuals are not considered surgical candidates. Alternative treatment options such as medications, intra-articular corticosteroid or hyaluronic acid injections, or radiofrequency nerve ablations can reduce pain and improve function in some individuals, but many others are left in a state of "orthopedic limbo": conservative therapies are insufficient, and surgery is not an option. Biologically based regenerative pain medicine therapies such as platelet-rich plasma (PRP) and autologous conditioned serum (ACS) offer new options for these patients and are used with increasing frequency in the United States. In this chapter, I will discuss the neuroimmune alterations that drive the development of osteoarthritis, the mechanisms of action of these biologically based, non-stem cell therapies, and clinical outcomes with the use of PRP and ACS.

Keywords Autologous conditioned serum (ACS) · Cytokines · Growth factors · Hyaluronic acid · Osteoarthritis (OA) · Platelet-rich plasma (PRP) · Regenerative therapies

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12.1 Introduction: Current Treatments for Osteoarthritis

The non-surgical management of patients with osteoarthritis (OA) of the knee or other joints follows a common pathway: physical therapy (PT), analgesic medications such as non-steroidal anti-inflammatory drugs (NSAIDs for topical and/or systemic uses) and acetaminophen, or procedures such as intra-articular corticosteroids (IA-C) and intra-articular hyaluronic acid (IA-HA). For patients with refractory pain, radiofrequency lesioning/destruction of the nerves that supply sensation to the joint is also considered. Of these modalities, PT and exercise remain critically important foundational therapies for any individual with degenerative joint disease. Exercise activates cartilage (chondrocytes) and tendon cells (tenocytes), increases collagen synthesis, and builds joint strength and stability (Hinterwimmer et al. 2004; O'Connor et al. 2015). Further, mechanical loading on joints has been shown to inhibit the production of inflammatory cytokines such as IL-1, reducing cartilage breakdown (Torzilli et al. 2010). For these reasons, PT and exercise should be part of all treatment plans.

Other treatments used for arthritis may not be as beneficial, however. For instance, NSAIDS carry significant risks: they have been shown to double the chances of kidney injury in individuals over the age of 65 and increase the risks for gastrointestinal bleeding and cardiovascular disease. Medication alternatives such as acetaminophen may be associated with lower kidney and GI toxicity but is often less effective than NSAIDS and may cause liver damage (Ong et al. 2007).

Injection techniques such as IA-C are performed several million times each year in the United States for the treatment of OA pain; although this procedure provides many patients with rapid analgesia, its benefits are generally short-lived, often lasting only a few weeks (Juni et al. 2015). When performed in a repeated fashion, IA-C also carries the risks of decreased bone density (Al-Shoha et al. 2012), immune system dysfunction (Sytsma et al. 2018), and cellular aging (Poulsen et al. 2014); there is also now clear evidence that repeated IA-C injections will accelerate cartilage loss and worsen joint damage (McAlindon et al. 2017).

IA-HA is another procedure frequently used for patients with OA. Hyaluronic acid, a normal part of synovial fluid, breaks down into smaller, less viscous molecules in arthritis. In efforts to improve joint viscosity, reinjection of HA has been a common procedure since the 1990s for these individuals (Temple-Wong et al. 2016). Hyaluronic acid, manufactured from rooster combs or bacterial sources, has been shown to be effective: a 2006 Cochrane review of 76 studies demonstrated improved pain and function for several months following IA-HA (Bellamy et al. 2006). Subsequent meta-analyses support both the clinical effectiveness for up to 6 months and the superiority to IA-C (Campbell et al. 2015a; He et al. 2017). IA-HA, however, often provides only modest improvements in pain and function for many patients, prompting major societies such as the American Academy of Orthopedic Surgeons and the American College of Rheumatology to recommend against the use of this procedure for the routine treatment of knee OA pain (Jevsevar 2013; Kolasinski et al. 2020). These guidelines, however, do not consider the beneficial

biological functions of IA-HA including the reduction of inflammatory cytokines such as IL-1β, TNFα, and IL-6, and a decrease in joint-damaging enzymes such as matrix metalloproteinases (MMP) (Nicholls et al. 2017). Further, HA increases the synthesis of beneficial cartilage proteoglycan, extracellular matrix proteins, and tissue inhibitors of metalloproteinases (TIMPs) (Campo et al. 2012; Nicholls et al. 2017; Waddell et al. 2007). These biologic activities appear to be magnified with the use of higher molecular weight products (Bowman et al. 2018), and may confer longer-term health benefits to the joint.

The other non-surgical procedure that has gained popularity for the treatment of OA pain (particularly the knee) is the use of geniculate radiofrequency lesioning (RFL) to ablate and reduce the nerve supply to the joint. This procedure has been shown to provide better pain relief than IA-C at 3 months (Chen et al. 2020b) and IA-HA at 6 months (Chen et al. 2020a) but does carry limitations; nerve ablation may decrease joint position sense, one of the important goals of many physical therapy and rehabilitation programs. If effective, RFL may need to be repeated every 10–12 months to maintain analgesia. I generally recommend this procedure for patients with end-stage OA who are not surgical candidates or for those who have persistent pain after joint replacement surgery.

Although these interventions may help, they are insufficient to treat the millions of adults in the United States with functional limitations from OA who are not surgical candidates (Hootman et al. 2016). Many patients remain in "orthopedic limbo": their pain is not significantly improved by traditional non-surgical treatments and their arthritis is not severe enough to require joint replacement surgery. Non-cellular biologic therapies such as PRP and ACS may offer additional analgesic benefits to these individuals through modulation of neuroimmune mechanisms.

12.2 Dissociation of Pain and Degeneration

The diagnosis of OA is based on standardized radiologic criteria such as the Kellgren–Lawrence (K–L) scale that includes four different categories of x-ray findings:

Grade 1, doubtful narrowing of joint space and possible osteophytic lipping
Grade 2, definite osteophytes and possible narrowing of joint space
Grade 3, moderate multiple osteophytes, definite narrowing of joints space, some sclerosis, and possible deformity of bone contours; and
Grade 4, large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contours

Although the K–L grading system has been used as the gold standard for OA diagnosis for over 50 years, almost ½ of individuals who meet these criteria for knee arthritis report little or no pain (Hannan et al. 2000). Similarly, while the prevalence of radiographic hip OA in individuals over the age of 50 is nearly 20%, only about 4% experience significant symptoms (Kim et al. 2014). This dramatic disconnect

between anatomy and symptoms challenges the validity of traditional diagnostic criteria and necessitates that we revisit the drivers of pain in OA. Although central sensitization is clearly a factor in regulating the severity of pain with any degenerative condition (Arendt-Nielsen 2017), central modulation is not sufficient to explain the diversity of symptom experiences, particularly in patients with bilateral disease but only unilateral pain (Barreto et al. 2019) or the absence of pain with advanced "bone on bone" OA. In these circumstances, peripheral biochemical alterations clearly play a dominant role in defining the severity of OA symptoms.

12.3 The Link Between Neuroinflammatory Mediators and Pain

Overexpression of inflammatory cytokines such as IL-1β, IL-6, and TNFα plays a prominent role in the initiation of degenerative joint disease (Martel-Pelletier et al. 1992), and the severity of pain in OA correlates with several of these proteins (Cuellar et al. 2009). Although cytokines likely play a diminished role for pain as OA advances (Orita et al. 2011), their early activities induce the production of catabolic enzymes such as matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) causing both joint erosion and neural sensitization (Adams et al. 2015; Goldring and Otero 2011; Nicholls et al. 2017; Pujol et al. 2009; Vandooren et al. 2014). MMP has several subtypes (MMP-1, MMP-3, MMP-13) that are found in higher concentrations in patients with arthritis (Yoshihara et al. 2000); likewise, ADAMTS type 4 and 5 are particularly damaging to joint cartilage (Yang et al. 2017). This catabolic cascade is further magnified by a parallel loss of growth factors such as TGF-β, FGF, IGF, HGF and protective cytokines such as IL-1 receptor antagonist (IL-1Ra) (Arend et al. 1998; Pujol et al. 2009). The composite of these biochemical activities ultimately leads to joint space narrowing, osteophyte overgrowth, and the radiographic diagnosis of OA (Blasioli and Kaplan 2014). The observed cytokine dysregulation in OA has led to several medication trials of disease-modifying antirheumatic drugs (DMARDs) in an attempt to slow or halt disease progression; unfortunately, these drugs have been largely ineffective in improving pain and symptoms (Chevalier et al. 2009; Chevalier et al. 2015). Effective, longer-term treatments for OA must address the complex biochemical alterations that lead to OA progression.

12.4 The Biochemistry of a Healthy Joint

Although no single cytokine appears able to reverse the catabolic cascade of OA, several are capable of improving the inflammatory changes of early OA and reducing pain (Pujol et al. 2009). IL-1Ra binds to the IL-1 receptor but does not induce a intracellular response, thereby inhibiting the damaging effects of this cytokine

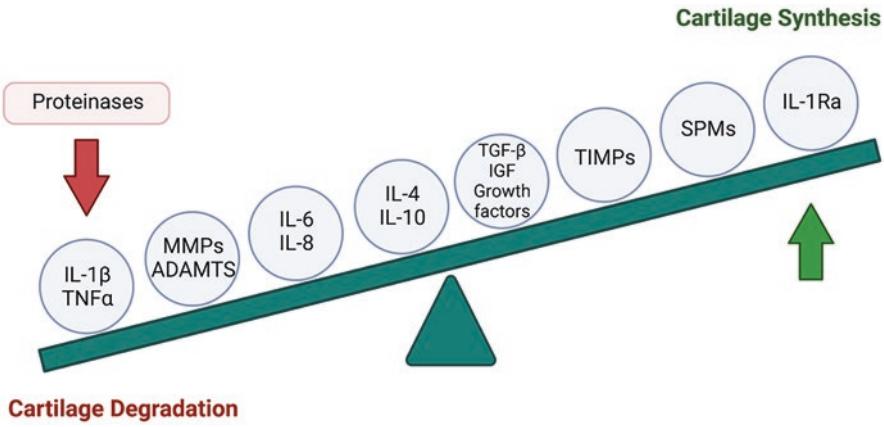

Fig. 12.1 Cytokines, growth factors, and MMP need to be in balance to maintain joint health. Cytokines such as IL-1 and TNF, and enzymes such as MMPs worsen cartilage damage; anabolic factors such as TGF-β and IL-1Ra augment the synthetic capacity of the synovial fluid and joint

(Arend et al. 1998). IL-10 is released by exercise and can both reduce pain and resolve inflammation following injury (da Silva et al. 2015; Grace et al. 2016; Sloane et al. 2009). Growth factors are also a critical component of healthy joints, promoting both collagen and proteoglycan production. In particular, TGF-β plays an important role in additionally reducing neuroinflammation and pain (Chen et al. 2015; Echeverry et al. 2009). The final category of proteins necessary for biochemical balance of the synovial fluid are TIMPS (the inhibitors of MMP and ADAMTS). TIMPS perform a vital role in controlling levels of enzymatic tissue breakdown, thereby offering joint and articular surface protection (Nakamura et al. 2020; Yoshihara et al. 2000). The healthy joint needs these protective cytokines, anabolic growth factors, and enzyme inhibitors to work in concert to maintain (or re-establish) function and reduce pain. This balance is illustrated in Fig. 12.1.

12.5 The Spectrum of Regenerative Therapies

Regenerative pain medicine encompasses a diversity of both "biologic" and "non-biologic" treatments. Common non-biologically based therapies include procedures such as surgical microfracturing, tendon fenestration, and prolotherapy. In surgical microfracturing, multiple lesions are created in the bone surface at the site of cartilage injury; this procedure has been shown to induce both cartilage growth and clinical improvements in the treated joint (Bae et al. 2006). Tendon fenestration employs a parallel process, where multiple needle passes create microinjury and induce the proliferative phase of healing in a chronic tendon injury (Jacobson et al. 2016). Prolotherapy uses a combination of both chemical and mechanical processes to produce controlled inflammation and induction of endogenous healing

mechanisms in the target structure (Topol et al. 2011). In contrast, the biologically based treatments rely on neuroimmune mechanisms rather than physical or chemical methods to induce tissue recovery, and include both cellular (stem cells) and non-cellular (PRP and ACS) interventions. This chapter will present the non-cellular treatments, their mechanisms of action, and their clinical effects in the treatment of osteoarthritis.

12.5.1 Platelet-Rich Plasma (PRP)

PRP has been used clinically since the 1980s when it was found that platelet concentrates stimulated wound healing after surgery (Alves and Grimalt 2018). Platelets contain over 300 growth factors such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblastic growth factor (FGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and others (Blair and Flaumenhaft 2009; Hickey et al. 2003; Xie et al. 2014). In most PRP preparations, white blood cells (WBCs) such as neutrophils and monocytes are also present in varying concentrations. WBC concentrations may increase levels of pro-inflammatory cytokines (Andia and Maffulli 2013), but also play a role in inducing the healing cascade after injection. This progression of cellular activities after tissue injury is shown in Fig. 12.2.

PRP contains additional anabolic factors such as tissue inhibitors of metalloproteases (TIMP-1, TIMP-2, TIMP-3, and TIMP-4) that promote cellular proliferation, matrix formation, and collagen synthesis (Rughetti et al. 2008). The secreted growth factors such as TGF-β, FGF, and IGF are also capable of recruiting endogenous hematopoietic stem cells and progenitor cells to the site, furthering tissue restoration (Baay et al. 2011; Crane and Cao 2014; Le Blanc and Mougiakakos 2012). Several classification systems have been proposed to characterize the PRP products, describing platelet counts, neutrophil, monocyte and growth factor concentrations, and other variables (Lana et al. 2017); ongoing research continues to define the optimal characteristics of PRP for various disorders. Two general methods of preparation include a "buffy coat" system and a "plasma-based" system. The buffy coat system is named after the appearance of plasma following centrifugation: there remains a "whitish" layer (the "buffy coat") on top of the red cells. These systems typically use a single, longer centrifugation process to isolate the platelet layer and often contain a higher concentration of platelets and WBCs.

With a plasma-based process for PRP, two shorter centrifugation steps are often performed; the initial centrifugation (a "soft spin") keeps platelets in plasma suspension; this plasma suspension subsequently undergoes a second spin to isolate the platelets. This method often reduces the WBC concentrations in PRP (and the potential for post-injection inflammatory pain) (Braun et al. 2014; Riboh et al. 2016); however, it also has the potential to reduce platelet counts and growth factor concentrations (Fig. 12.3).

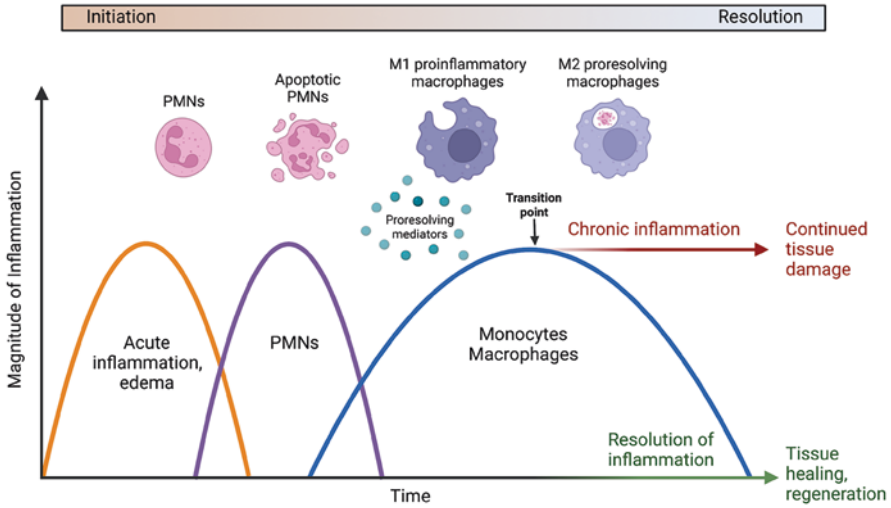

Fig. 12.2 Injury induces platelet activation and the release of growth factors and chemokines on the left. Neutrophils, the most common WBC in circulation initially respond; they are followed by monocytes/macrophages that migrate to the area and begin the transition to an M2 pro-resolving phenotype. This M2 macrophage is capable of releasing growth factors and anabolic cytokines that resolve chronic inflammation and induce tissue healing

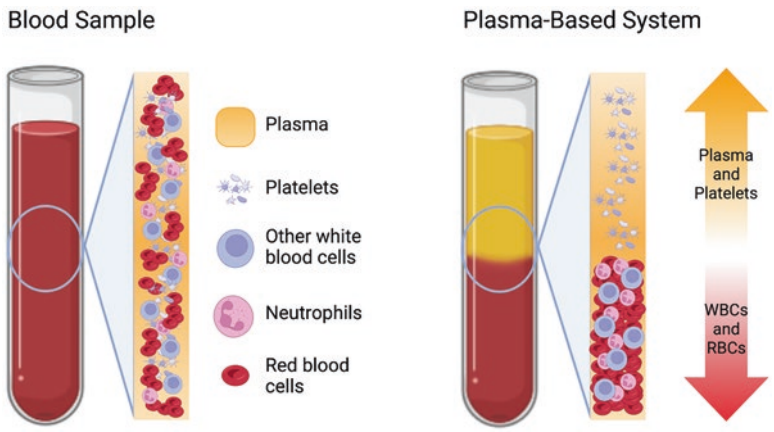

Fig. 12.3 "Plasma" process for PRP. (**a**). Whole blood is collected with anticoagulant and briefly centrifuged with low centrifugal forces (a "softspin"). This process keeps many of the platelets in plasma suspension. (**b**). This plasma suspension then undergoes a second spin to concentrate the platelets. Most of the PPP is then removed, and the platelets re-suspended in the remaining plasma for the final PRP preparation

PRP-based growth factors such as TGF-β, PDGF, IGF, FGF, EGF, VEGF, and HGF have been shown to produce multiple beneficial effects including the reduction of inflammatory cytokines such as IL-1β. The activation of NFκB, a critical

transcription factor for immune and inflammatory processes, is also minimized in osteoarthritic chondrocytes through suppression of CXCR4 in surrounding monocytes/macrophages (Bendinelli et al. 2010; Blair and Flaumenhaft 2009; Hickey et al. 2003; van Buul et al. 2011; Xie et al. 2014). TGF-β and other growth factors additionally promote collagen and proteoglycan production, and chondrocyte proliferation (Akeda et al. 2006; J.-P. Pujol et al. 2009; Sun et al. 2010; van Buul et al. 2011; Wu et al. 2011). PRP-based TIMPs suppress the activity of catabolic enzymes such as MMP3, MMP 13, and ADAMTS, preserving cartilage (Rughetti et al. 2008; Sundman et al. 2014). Collectively, these activities have been shown to enhance cartilage and meniscal cell regeneration in animal models (Ishida et al. 2007; Kwon et al. 2012); however, radiographic restoration of cartilage does not appear to be significant when measured in in human trials (Hart et al. 2013). In addition to direct growth factor and cytokine effects, PRP has been shown to increase endogenous hyaluronic acid secretion in arthritis patients (Anitua et al. 2007), with presumptive improvements in synovial fluid viscosity (Detterline et al. 2008). Overall, PRP appears to improve the health of existing cartilage and tissues by reducing concentrations of damaging cytokines and catabolic enzymes, augmenting beneficial cytokines and growth factors, and promoting endogenous hyaluronic acid production.

The majority of clinical trials of PRP have been in the treatment of knee osteoarthritis where reductions in pain and improvements in function have been demonstrated by both cohort studies (Halpern et al. 2013) and randomized controlled trials (Patel et al. 2013; Sánchez et al. 2012; Vaquerizo et al. 2013). Meta-analyses and systematic reviews additionally support the use of PRP for mild to moderate OA, finding superiority of PRP to IA-HA at 12 months or greater and level I evidence for pain reduction at this period (Belk et al. 2020; Campbell et al. 2015b; Chang et al. 2014; Dai et al. 2017; Johal et al. 2019; Meheux et al. 2016; Sadabad et al. 2016). However, the superiority of PRP over IA-HA has not been noted in all trials (Di Martino et al. 2019; Filardo et al. 2015), leading to an ongoing debate as to the optimal PRP preparation methods and WBC concentrations (Belk et al. 2020). It has been further demonstrated that low platelet PRP products have limited effectiveness in the treatment of knee OA (Bennell et al. 2021). The first randomized comparative trial between PRP and bone marrow stem cells was performed in 2020; the interventions were both found to be effective at 12 months and no difference in outcome was seen between the treatment methods (Anz et al. 2020). The benefits of PRP appear to be greatest in younger patients with earlier stage disease (Chang et al. 2014; Halpern et al. 2013; Patel et al. 2013), likely because of greater autologous growth factor concentrations and fewer senescent chondrocytes. Interestingly, although the impact of hyaluronic acid injection by itself may be modest, there is growing evidence that IA-HA enhances the benefits of PRP by further inhibiting MMP and acting as a matrix for anabolic PRP activities (Chen et al. 2014; Dai et al. 2017; Privata et al. 2019; Zhao et al. 2020).

PRP has also been studied for the treatment of tendinopathy; pre-clinical data reveal that the injection of PRP-based growth factors such as TGFβ and VEGF increases the strength of healing tendons (Docheva et al. 2015; Rodik and

McDermott 2016). Clinically, PRP demonstrates good longer-term outcomes for patients with lateral epicondylopathy (Gosens et al. 2011; Johal et al. 2019; Mishra et al. 2014; Peerbooms et al. 2010) faster recovery of ACL after surgery (Seijas et al. 2013), and evidence of improved tendon healing after injury (Gautam et al. 2015). In a randomized trial, PRP was shown to be superior to dry needling in rotator cuff disease (Rha et al. 2013); however, positive results with the use of PRP in rotator cuff tendinopathy are not universal (Kesikburun et al. 2013; Rha et al. 2013; Schwitzguebel et al. 2019). A 2016 meta-analysis of 18 studies further supports the use of ultrasound-guided PRP in the treatment of chronic tendinopathies of multiple locations (Fitzpatrick et al. 2017), although definitive conclusions and indications for PRP use with various tendinopathies are still being clarified.

12.5.2 Autologous Conditioned Serum (ACS)

Whole blood incubation techniques have also been explored as a method to augment beneficial cytokines and anabolic growth factors. Initial research in this process was performed in Germany and the United States in the 1990s, with the subsequent development of ACS (Evans 2005; Wehling et al. 2007). ACS is now used throughout Europe and in several sites in the United States (Evans et al. 2016). In contrast to PRP, ACS is a filtered serum product without platelets or other cellular components (Evans et al. 2016) (Fig. 12.4).

The ACS incubation process has been shown to significantly increase levels of anti-inflammatory cytokines such as IL-1Ra, IL-4, and IL-10, as well as TGFβ, a critical growth factor for cartilage and tissue health (Evans et al. 2016). When used in animal models, ACS produces thickening of tendons, higher concentrations of type I collagen, and decreases in synovial hyperplasia (Frisbie et al. 2007). In addition to the important induction of cytokines and growth factors in ACS, it also appears that extracellular vesicles such as exosomes may play a vital role in the prolonged analgesia that is observed after injection (Shirokova et al. 2020). The role of exosomes in biologically based therapies remains an active area of investigation.

Initial published use of ACS for the treatment of knee arthritis pain included 1000 patients as part of a prospective, observational trial; WOMAC scores improved by 75% in >70% of patients (Baltzer et al. 2003). A large, blinded, randomized controlled trial (RCT) in 2009 demonstrated superior clinical outcomes of ACS over IA-HA and placebo, and improvements were maintained for at least 2 years (Baltzer et al. 2009). A smaller RCT by Yang et al. was also performed in patients with knee OA; the primary outcome measure of this study did not reach significance; however, the investigators noted that KOOS scores were significantly improved in the ACS group at 12 months in comparison to the saline injections (Yang et al. 2008). The benefits of ACS are further supported by a 2-year observational trial of 118 patients who experienced a 62% decrease in VAS scores and a 56% decrease in WOMAC scores at follow-up (García-Escudero and Trillos 2015). Positive observational

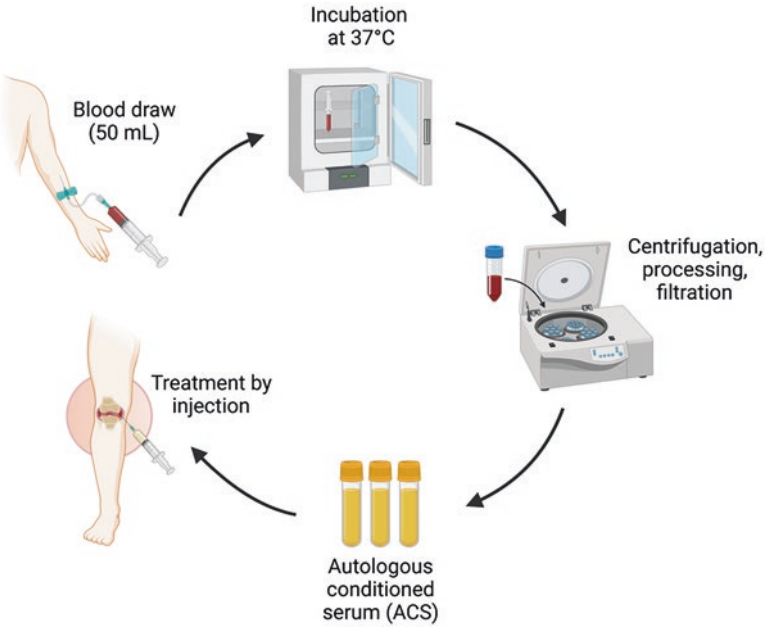

Fig. 12.4 Autologous conditioned serum. Whole blood is incubated under controlled conditions, centrifuged, processed, filtered, and then used for injection

results have also been noted with the use of ACS for hip arthritis (Baltzer et al. 2013), rotator cuff pathology (Damjanov et al. 2018), and Achilles tendinopathy (von Wehren et al. 2019). As a surgical adjuvant, ACS appears to improve outcomes of ACL reconstruction, providing superior WOMAC and IKDC scores compared to the control patients and significant decreases in the synovial fluid levels of IL-1 (Darabos et al. 2011).

12.6 Conclusions

It is increasingly clear that neuroimmune mechanisms drive symptoms in OA and the biochemical imbalance that leads to disease progression is significantly responsive to regenerative pain therapies. Despite the multitude of processing techniques, there are common analgesic mechanisms that these therapies share, including the enhancement of growth factors and anabolic cytokines. PRP and ACS have been used for decades and demonstrate superiority to standard treatments such as steroid or IA-HA injection, not only reducing symptoms, but potentially modifying disease course. As research continues to clarify optimal processing methods and disease-specific indications, the roles for these biologically based interventions will continue to expand in the non-surgical treatment of osteoarthritis.

References

Adams SB, Setton LA, Bell RD, Easley ME, Huebner JL, Stabler T, Kraus VB, Leimer EM, Olson SA, Nettles DL. Inflammatory cytokines and matrix metalloproteinases in the synovial fluid after intra-articular ankle fracture. Foot Ankle Int. 2015;36(11):1264–71.

Akeda K, An HS, Okuma M, Attawia M, Miyamoto K, Thonar EJMA, Lenz ME, Sah RL, Masuda K. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthr Cartil. 2006;14(12):1272–80.

Al-Shoha A, Rao DS, Schilling J, Peterson E, Mandel S. Effect of epidural steroid injection on bone mineral density and markers of bone turnover in postmenopausal women. Spine (Phila Pa 1976). 2012;37(25):E1567–71.

Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Append Disord. 2018;4(1):18–24.

Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nat Rev Rheumatol. 2013;9(12):721–30.

Anitua E, Sanchez M, Nurden AT, Zalduendo MM, de la Fuente M, Azofra J, Andia I. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology (Oxford). 2007;46(12):1769–72.

Anz AW, Hubbard R, Rendos NK, Everts PA, Andrews JR, Hackel JG. Bone marrow aspirate concentrate is equivalent to platelet-rich plasma for the treatment of knee osteoarthritis at 1 year: a prospective, randomized trial. Orthop J Sports Med. 2020;8(2):2325967119900958.

Arend WP, Malyak M, Guthridge CJ, Gabay C. Interleukin-1 receptor antagonist: role in biology. Annu Rev Immunol. 1998;16:27–55.

Arendt-Nielsen L. Joint pain: more to it than just structural damage? Pain. 2017;158(Suppl 1):S66–73.

Baay M, Brouwer A, Pauwels P, Peeters M, Lardon F. Tumor cells and tumor-associated macrophages: secreted proteins as potential targets for therapy. Clin Dev Immunol. 2011;2011:565187.

Bae DK, Yoon KH, Song SJ. Cartilage healing after microfracture in osteoarthritic knees. Arthroscopy. 2006;22(4):367–74.

Baltzer ADR, Granrath M, et al. Intra-articular treatment of osteoarthritis using autologous interleukin-1 receptor antagonist (il1-ra) conditioned serum. Dtsch Z Sportmed. 2003;54:209–11.

Baltzer AWA, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (orthokine) is an effective treatment for knee osteoarthritis. Osteoarthr Cartil. 2009;17(2):152–60.

Baltzer AWA, Ostapczuk MS, Stosch D, Seidel F, Granrath M. A new treatment for hip osteoarthritis: clinical evidence for the efficacy of autologous conditioned serum. Orthop Rev (Pavia). 2013;5(2):e13.

Barreto RPG, Braman JP, Ludewig PM, Ribeiro LP, Camargo PR. Bilateral magnetic resonance imaging findings in individuals with unilateral shoulder pain. J Shoulder Elb Surg. 2019;28(9):1699–706.

Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Am J Sports Med.363546520909397. 2020.

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. (2):CD005321. 2006.

Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, Desiderio MA. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of nf-kappab inhibition via hgf. J Cell Physiol. 2010;225(3):757–66.

Bennell K, Paterson B, Metcalf V, Duong J, Eyles J, Kasza Y, Wang F, Cicuttini R, Buchbinder A, Forbes A, Harris S, Yu D, Connell J, Linklater B, Wang W, Oo M, Hunter D. Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial Tibial cartilage volume in patients with knee osteoarthritis: the RESTORE randomized clinical trial. JAMA. 2021;326(20):2021–30.

Blair P, Flaumenhaft R. Platelet alpha-granules: basic biology and clinical correlates. Blood Rev. 2009;23(4):177–89.

Blasioli DJ, Kaplan DL. The roles of catabolic factors in the development of osteoarthritis. Tissue Eng Part B Rev. 2014;20(4):355–63.

Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. Clin Transl Med. 2018;7(1):6.

Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes. Am J Sports Med. 2014;42(5):1204–10.

Campbell KA, Erickson BJ, Saltzman BM, Mascarenhas R, Bach BR Jr, Cole BJ, Verma NN. Is local viscosupplementation injection clinically superior to other therapies in the treatment of osteoarthritis of the knee: a systematic review of overlapping meta-analyses. Arthroscopy. 2015a;31(10):2036–45.

Campbell KA, Saltzman BM, Mascarenhas R, Khair MM, Verma NN, Bach BR Jr, Cole BJ. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. Arthroscopy. 2015b;31(11):2213–21.

Campo GM, Avenoso A, D'Ascola A, Prestipino V, Scuruchi M, Nastasi G, Calatroni A, Campo S. Hyaluronan differently modulates tlr-4 and the inflammatory response in mouse chondrocytes. Biofactors. 2012;38(1):69–76.

Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2014;95(3):562–75.

Chen WH, Lo WC, Hsu WC, Wei HJ, Liu HY, Lee CH, Tina Chen SY, Shieh YH, Williams DF, Deng WP. Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. Biomaterials. 2014;35(36):9599–607.

Chen G, Park CK, Xie RG, Ji RR. Intrathecal bone marrow stromal cells inhibit neuropathic pain via tgf-beta secretion. J Clin Invest. 2015;125(8):3226–40.

Chen AF, Khalouf F, Zora K, DePalma M, Kohan L, Guirguis M, Beall D, Loudermilk E, Pingree M, Badiola I, et al. Cooled radiofrequency ablation compared with a single injection of hyaluronic acid for chronic knee pain: a multicenter, randomized clinical trial demonstrating greater efficacy and equivalent safety for cooled radiofrequency ablation. J Bone Joint Surg Am. 2020a;102(17):1501–10.

Chen AF, Mullen K, Casambre F, Visvabharathy V, Brown GA. Thermal nerve radiofrequency ablation for the nonsurgical treatment of knee osteoarthritis: a systematic literature review. J Am Acad Orthop Surg. 2020b.

Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, Loeuille D, Kivitz AJ, Silver D, Appleton BE. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2009;61(3):344–52.

Chevalier X, Ravaud P, Maheu E, Baron G, Rialland A, Vergnaud P, Roux C, Maugars Y, Mulleman D, Lukas C, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and nsaids: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis. 2015;74(9):1697–705.

Crane JL, Cao X. 2014. Bone marrow mesenchymal stem cells and tgf-β signaling in bone remodeling. J Clin invest. 124(2):466-472-472.

Cuellar JM, Scuderi GJ, Cuellar VG, Golish SR, Yeomans DC. 2009. Diagnostic utility of cytokine biomarkers in the evaluation of acute knee pain. The journal of Bone & Joint Surgery. 91(10):2313-2320-2320.

da Silva MD, Bobinski F, Sato KL, Kolker SJ, Sluka KA, Santos AR. Il-10 cytokine released from m2 macrophages is crucial for analgesic and anti-inflammatory effects of acupuncture in a model of inflammatory muscle pain. Mol Neurobiol. 2015;51(1):19–31.

Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Arthroscopy. 2017;33(3):659–70.

Damjanov N, Barac B, Colic J, Stevanovic V, Zekovic A, Tulic G. The efficacy and safety of autologous conditioned serum (acs) injections compared with betamethasone and placebo injections in the treatment of chronic shoulder joint pain due to supraspinatus tendinopathy: a prospective, randomized, double-blind, controlled study. Med Ultrason. 2018;20(3):335–41.

Darabos N, Haspl M, Moser C, Darabos A, Bartolek D, Groenemeyer D. Intraarticular application of autologous conditioned serum (acs) reduces bone tunnel widening after acl reconstructive surgery in a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2011;19(Suppl 1):S36–46.

Detterline AJ, Goldstein JL, Rue JP, Bach BR Jr. Evaluation and treatment of osteochondritis dissecans lesions of the knee. J Knee Surg. 2008;21(2):106–15.

Di Martino A, Di Matteo B, Papio T, Tentoni F, Selleri F, Cenacchi A, Kon E, Filardo G. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. Am J Sports Med. 2019;47(2):347–54.

Docheva D, Muller SA, Majewski M, Evans CH. Biologics for tendon repair. Adv Drug Deliv Rev. 2015;84:222–39.

Echeverry S, Shi XQ, Haw A, Liu H, Zhang ZW, Zhang J. Transforming growth factor-beta1 impairs neuropathic pain through pleiotropic effects. Mol Pain. 2009;5:16.

Evans CH. Novel biological approaches to the intra-articular treatment of osteoarthritis. Biodrugs. 2005;19(6):355–62.

Evans CH, Chevalier X, Wehling P. Autologous conditioned serum. Phys Med Rehabil Clin N Am. 2016;27(4):893–908.

Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. Am J Sports Med. 2015;43(7):1575–82.

Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. Am J Sports Med. 2017;45(1):226–33.

Frisbie DD, Kawcak CE, Werpy NM, Park RD, McIlwraith CW. Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. Am J Vet Res. 2007;68(3):290–6.

García-Escudero JB, Trillos PMH. Treatment of osteoarthritis of the knee with a combination of autologous conditioned serum and physiotherapy: a two-year observational study. PLoS One. 2015;10(12):e0145551.

Gautam VK, Verma S, Batra S, Bhatnagar N, Arora S. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: clinical and ultrasonographic evaluation. J Orthop Surg (Hong Kong). 2015;23(1):1–5.

Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol. 2011;23(5):471–8.

Gosens T, Peerbooms JC, Laar WV, Oudsten BLD. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis. The American Journal of Sports Medicine. 2011;39(6):1200–8.

Grace PM, Fabisiak TJ, Green-Fulgham SM, Anderson ND, Strand KA, Kwilasz AJ, Galer EL, Walker FR, Greenwood BN, Maier SF, et al. Prior voluntary wheel running attenuates neuropathic pain. Pain. 2016;157(9):2012–23.

Halpern B, Chaudhury S, Rodeo SA, Hayter C, Bogner E, Potter HG, Nguyen J. Clinical and mri outcomes after platelet-rich plasma treatment for knee osteoarthritis. Clin J Sport Med. 2013;23(3):238–9.

Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol. 2000;27(6):1513–7.

Hart R, Safi A, Komzak M, Jajtner P, Puskeiler M, Hartova P. Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. Arch Orthop Trauma Surg. 2013;133(9):1295–301.

He WW, Kuang MJ, Zhao J, Sun L, Lu B, Wang Y, Ma JX, Ma XL. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: a meta-analysis. Int J Surg. 2017;39:95–103.

Hickey DG, Frenkel SR, Di Cesare PE. Clinical applications of growth factors for articular cartilage repair. Am J Orthop (Belle Mead NJ). 2003;32(2):70–6.
Hinterwimmer S, Krammer M, Krötz M, Glaser C, Baumgart R, Reiser M, Eckstein F. Cartilage atrophy in the knees of patients after seven weeks of partial load bearing. Arthritis Rheum. 2004;50(8):2516–20.
Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among us adults, 2015-2040. Arthritis Rheumatol. 2016;68(7):1582–7.
Ishida K, Kuroda R, Miwa M, Tabata Y, Hokugo A, Kawamoto T, Sasaki K, Doita M, Kurosaka M. The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. Tissue Eng. 2007;13(5):1103–12.
Jacobson JA, Yablon CM, Henning PT, Kazmers IS, Urquhart A, Hallstrom B, Bedi A, Parameswaran A. Greater trochanteric pain syndrome: percutaneous tendon fenestration versus platelet-rich plasma injection for treatment of gluteal tendinosis. J Ultrasound Med. 2016;35(11):2413–20.
Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg. 2013;21(9):571–6.
Johal H, Khan M, Yung SP, Dhillon MS, Fu FH, Bedi A, Bhandari M. Impact of platelet-rich plasma use on pain in orthopaedic surgery: a systematic review and meta-analysis. Sports Health. 2019;11(4):355–66.
Juni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, da Costa BR. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev. 2015;10:CD005328.
Kesikburun S, Tan AK, Yılmaz B, Yaşar E, Yazıcıoğlu K. 2013. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy. The American journal of sports medicine. 41(11):2609-2616-2616.
Kim C, Linsenmeyer KD, Vlad SC, Guermazi A, Clancy MM, Niu J, Felson DT. Prevalence of radiographic and symptomatic hip osteoarthritis in an urban United States community: the Framingham osteoarthritis study. Arthritis Rheumatol. 2014;66(11):3013–7.
Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020;72(2):220–33.
Kwon DR, Park GY, Lee S-u. The effects of intra-articular platelet-rich plasma injection according to the severity of collagenase-induced knee osteoarthritis in a rabbit model. Ann Rehabil Med. 2012;36(4):458–65.
Lana JFSD, Purita J, Paulus C, Huber SC, Rodrigues BL, Rodrigues AA, Santana MH, Luzo ÂCM, Belangero WD, et al. Contributions for classification of platelet rich plasma – proposal of a new classification: Marspill. Regen Med. 2017;12:565.
Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II Arthritis Rheum. 2008;58(1):26–35.
Le Blanc K, Mougiakakos D. Multipotent mesenchymal stromal cells and the innate immune system. Nat Rev Immunol. 2012;12(5):383–96.
Martel-Pelletier J, McCollum R, DiBattista J, Faure MP, Chin JA, Fournier S, Sarfati M, Pelletier JP. The interleukin-1 receptor in normal and osteoarthritic human articular chondrocytes. Identification as the type i receptor and analysis of binding kinetics and biologic function. Arthritis Rheum. 1992;35(5):530–40.
McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, Ward RJ. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA. 2017;317(19):1967–75.
Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. 2016. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. Arthroscopy. 32(3):495-505-505.

Mishra AK, Skrepnik NV, Edwards SG, Jones GL, Sampson S, Vermillion DA, Ramsey ML, Karli DC, Rettig AC. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sports Med. 2014;42(2):463–71.

Nakamura H, Vo P, Kanakis I, Liu K, Bou-Gharios G. Aggrecanase-selective tissue inhibitor of metalloproteinase-3 (timp3) protects articular cartilage in a surgical mouse model of osteoarthritis. Sci Rep. 2020;10(1):9288.

Nicholls MA, Fierlinger A, Niazi F, Bhandari M. The disease-modifying effects of hyaluronan in the osteoarthritic disease state. Clin Med Insights Arthritis Musculoskelet Disord. 2017;10:1179544117723611.

O'Connor SR, Tully MA, Ryan B, Bleakley CM, Baxter GD, Bradley JM, McDonough SM. Walking exercise for chronic musculoskeletal pain: systematic review and meta-analysis. Arch Phys Med Rehabil. 2015;96(4):724–34. e723

Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res. 2007;5(1):19–34.

Orita S, Koshi T, Mitsuka T, Miyagi M, Inoue G, Arai G, Ishikawa T, Hanaoka E, Yamashita K, Yamashita M, et al. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. BMC Musculoskelet Disord. 2011;12:144.

Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013;41(2):356–64.

Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med. 2010;38(2):255–62.

Poulsen RC, Watts AC, Murphy RJ, Snelling SJ, Carr AJ, Hulley PA. Glucocorticoids induce senescence in primary human tenocytes by inhibition of sirtuin 1 and activation of the p53/p21 pathway: in vivo and in vitro evidence. Ann Rheum Dis. 2014;73(7):1405–13.

Pujol J-P, Chadjichristos C, Legendre F, Baugé C, Beauchef G, Andriamanalijaona R, Galéra P, Boumediene K. Interleukin-1 and transforming growth factor-ß 1 as crucial factors in osteoarthritic cartilage metabolism. Connect Tissue Res. 2009;49(3-4):293–7.

Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil. 2013;27(2):113–22.

Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. Am J Sports Med. 2016;44(3):792–800.

Rodik T, McDermott B. Platelet-rich plasma compared with other common injection therapies in the treatment of chronic lateral epicondylitis. J Sport Rehabil. 2016;25(1):77–82.

Rughetti A, Giusti I, D'Ascenzo S, Leocata P, Carta G, Pavan A, Dell'Orso L, Dolo V. Platelet gel-released supernatant modulates the angiogenic capability of human endothelial cells. Blood Transfus. 2008;6(1):12–7.

Sadabad HN, Behzadifar M, Arasteh F, Behzadifar M, Dehghan HR. Efficacy of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: a systematic review and meta-analysis. Electron Physician. 2016;8(3):2115–22.

Sánchez M, Fiz N, Azofra J, Usabiaga J, Recalde EA, Gutierrez AG, Albillos J, Gárate R, Aguirre JJ, Padilla S, et al. A randomized clinical trial evaluating plasma rich in growth factors (prgf-endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy. J Arthroscop Relat Surg. 2012;28(8):1070–8.

Schwitzguebel AJ, Kolo FC, Tirefort J, Kourhani A, Nowak A, Gremeaux V, Saffarini M, Ladermann A. Efficacy of platelet-rich plasma for the treatment of interstitial supraspinatus tears: a double-blinded, randomized controlled trial. Am J Sports Med. 363546519851097. 2019.

Seijas R, Ares O, Catala J, Alvarez-Diaz P, Cusco X, Cugat R. Magnetic resonance imaging evaluation of patellar tendon graft remodelling after anterior cruciate ligament reconstruction with or without platelet-rich plasma. J Orthopaed Surg. 2013;21(1):10–4.

Shirokova L, Noskov S, Gorokhova V, Reinecke J, Shirokova K. Intra-articular injections of a whole blood clot secretome, autologous conditioned serum, have superior clinical and biochemical efficacy over platelet-rich plasma and induce rejuvenation-associated changes of joint metabolism: a prospective, controlled open-label clinical study in chronic knee osteoarthritis. Rejuvenation Res. 2020;23(5):401–10.

Sloane EM, Soderquist RG, Maier SF, Mahoney MJ, Watkins LR, Milligan ED. Long-term control of neuropathic pain in a non-viral gene therapy paradigm. Gene Ther. 2009;16(4):470–5.

Sun Y, Feng Y, Zhang CQ, Chen SB, Cheng XG. The regenerative effect of platelet-rich plasma on healing in large osteochondral defects. Int Orthop. 2010;34(4):589–97.

Sundman EA, Cole BJ, Karas V, Della Valle C, Tetreault MW, Mohammed HO, Fortier LA. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med. 2014;42(1):35–41.

Sytsma TT, Greenlund LK, Greenlund LS. Joint corticosteroid injection associated with increased influenza risk. Mayo Clin Proc Innov Qual Outcomes. 2018;2(2):194–8.

Temple-Wong MM, Ren S, Quach P, Hansen BC, Chen AC, Hasegawa A, D'Lima DD, Koziol J, Masuda K, Lotz MK, et al. Hyaluronan concentration and size distribution in human knee synovial fluid: variations with age and cartilage degeneration. Arthritis Res Ther. 2016;18:18.

Topol GA, Podesta LA, Reeves KD, Raya MF, Fullerton BD, Yeh HW. Hyperosmolar dextrose injection for recalcitrant osgood-schlatter disease. Pediatrics. 2011;128(5):e1121–8.

Torzilli PA, Bhargava M, Park S, Chen CT. Mechanical load inhibits il-1 induced matrix degradation in articular cartilage. Osteoarthr Cartil. 2010;18(1):97–105.

van Buul GM, Koevoet WL, Kops N, Bos PK, Verhaar JA, Weinans H, Bernsen MR, van Osch GJ. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med. 2011;39(11):2362–70.

Vandooren J, Van Damme J, Opdenakker G. On the structure and functions of gelatinase b/matrix metalloproteinase-9 in neuroinflammation. Prog Brain Res. 2014;214:193–206.

Vaquerizo V, Plasencia MÁ, Arribas I, Seijas R, Padilla S, Orive G, Anitua E. Comparison of intra-articular injections of plasma rich in growth factors (prgf-endoret) versus durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. Arthroscop J Arthroscop Relat Surg. 2013;29(10):1635–43.

von Wehren L, Pokorny K, Blanke F, Sailer J, Majewski M. Injection with autologous conditioned serum has better clinical results than eccentric training for chronic achilles tendinopathy. Knee Surg Sports Traumatol Arthrosc. 2019.

Waddell DD, Kolomytkin OV, Dunn S, Marino AA. Hyaluronan suppresses il-1beta-induced metalloproteinase activity from synovial tissue. Clin Orthop Relat Res. 2007;465:241–8.

Wehling P, Moser C, Frisbie D, McIlwraith CW, Kawcak CE, Krauspe R, Reinecke JA. Autologous conditioned serum in the treatment of orthopedic diseases. Biodrugs. 2007;21(5):323–33.

Wu C-C, Chen W-H, Zao B, Lai P-L, Lin T-C, Lo H-Y, Shieh Y-H, Wu C-H, Deng W-P. Regenerative potentials of platelet-rich plasma enhanced by collagen in retrieving pro-inflammatory cytokine-inhibited chondrogenesis. Biomaterials. 2011;32(25):5847–54.

Xie X, Zhang C, Tuan RS. Biology of platelet-rich plasma and its clinical application in cartilage repair. Arthritis Res Ther. 2014;16(1):204.

Xix Congresso Nazionale S.I.C.O.O.P. Societa' Italiana Chirurghi Ortopedici Dell'Ospedalita' Privata A, Papalia R, Zampogna B, Russo F, Torre G, De Salvatore S, Nobile C, Tirindelli MC, Grasso A, Vadala G, et al. The combined use of platelet rich plasma and hyaluronic acid: Prospective results for the treatment of knee osteoarthritis. J Biol Regul Homeost Agents. 2019;33(2 Suppl. 1):21–8.

Yang KGA, Raijmakers NJH, ERAV A, Caron JJ, Rijk PC, Willems WJ, JAC Z, Verbout AJ, WJA D, DBF S. Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. Osteoarthritis Cartilage. 2008;16(4):498–505.

Yang CY, Chanalaris A, Troeberg L. Adamts and Adam metalloproteinases in osteoarthritis - looking beyond the 'usual suspects'. Osteoarthr Cartil. 2017;25(7):1000–9.

Yoshihara Y, Nakamura H, Obata K, Yamada H, Hayakawa T, Fujikawa K, Okada Y. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in synovial fluids from patients with rheumatoid arthritis or osteoarthritis. Ann Rheum Dis. 2000;59(6):455–61.

Zhao J, Huang H, Liang G, Zeng LF, Yang W, Liu J. Effects and safety of the combination of platelet-rich plasma (prp) and hyaluronic acid (ha) in the treatment of knee osteoarthritis: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2020;21(1):224.