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Autologous Protein Solution (nSTRIDE) as a Novel Therapeutic Option in Osteoarthritis: Implications for Clinical Practice

Jihad Abouali, MD, FRCSC

Introduction

Osteoarthritis (OA) is a disabling disease affecting hundreds of millions of people globally.[1] It develops through a combination of mechanical stress and aging, leading to chondrocyte dysfunction and an imbalance between matrix degradation and synthesis. This imbalance is driven by upregulation of matrix metalloproteinases and pro-inflammatory cytokines.[2] The joint degeneration causes inflammation, pain, limited mobility, and a negative impact on one's quality of life. There are a variety of treatments for OA, including lifestyle changes, physiotherapy, intra-articular injections, and more invasively, arthroplasty. Common intra-articular injections include corticosteroids, hyaluronic acid (HA), and platelet-rich plasma (PRP).

Corticosteroids

Corticosteroid injections have an analgesic effect in arthritis by exerting anti-inflammatory and immunosuppressive responses. They directly act by binding to nuclear steroid receptors, which initiates a complex that interrupts the inflammatory cascade. Additionally, these injections prevent the formation of pro-inflammatory mediators such as neutrophils, metalloproteases, and prostaglandins.[3] However, corticosteroid injections offer neither long-term efficacy nor functional improvements, and concerns remain regarding further cartilage damage.[4] The American Academy of Orthopedic Surgeons (AAOS) and European Society of Sports Traumatology, Knee Surgery, and Arthroscopy (ESSKA) advise caution regarding how soon surgery can be

performed on the joint after a steroid injection, with ESSKA recommending a minimum waiting period of at least 6 months.[5,6] These organizations also emphasize the short-lived benefits of corticosteroid injections, with ESSKA warning about their damaging effects on cartilage.[6]

Hyaluronic Acid

HA injections replace the naturally occurring substance found within the joint capsule. HA, a main component of synovial fluid and cartilage matrix, provides lubrication and shock absorption for the joint. These injections are thought to restore this viscoelastic substance within the joint capsule.[3] Recent literature, including a review by Bhandari et al.,[7] highlights the advantages of non-crosslinked high molecular weight HA in early intervention. This form of HA more effectively downregulates the CD44-mediated inflammatory response in chondrocytes and more closely mimics the viscoelastic properties of healthy synovial fluid, supporting joint function. These properties may offer greater therapeutic benefit in early-stage osteoarthritis compared to crosslinked formulations. The AAOS advises against routine use of HA injections for knee osteoarthritis because studies have not shown consistent, generalized benefit across all KL grades. Their guidance notes that any potential benefit is more likely in early-stage OA (lower KL grades), while patients with advanced OA (KL IV) tend to experience limited or no improvement.[8] However, ESSKA's review of injectable orthobiologics mentioned a study recommending the use of HA injections in conjunction with PRP injections.[9]

Platelet-rich Plasma

PRP injections are an autologous treatment for OA. These injections focus on concentrating platelets from the patient's blood by using centrifugation, producing a solution with significantly higher levels of anti-inflammatory cytokines and growth factors compared to baseline blood. Typical PRP preparation times can range from about 5–20 minutes depending on system type. PRP exerts its potential therapeutic effect in knee osteoarthritis through anabolic stimulation of chondrocytes, primarily via growth factors like IGF-1, which can enhance cartilage matrix synthesis and cell activity. While Leukocyte-Poor PRP (LP-PRP) was initially favoured based on in vitro studies showing a more favourable response in chondrocyte cultures,[10,11] an in vivo study by Filardo et al. demonstrated comparable clinical outcomes and safety between LP-PRP and Leukocyte-Rich PRP (LR-PRP) at 12 months.[12] Current ESSKA guidance supports the use of both LP-PRP and LR-PRP for knee OA, noting that LR-PRP is not clinically detrimental and may offer similar benefit in appropriately selected patients. The AAOS is neither in favour nor against these injections.

Autologous Protein Solution (nSTRIDE)

Autologous Protein Solution (APS), also known as nSTRIDE, is a novel approach to treating OA. Similar to PRP, it is derived from separating plasma, platelets, and white blood cells, but the contents of the two solutions differ in composition. Both APS and PRP are platelet-rich and contain large amounts of anti-inflammatory cytokines and growth factors; however, only APS contains high concentrations of white blood cells (WBC), a source of anti-inflammatory cytokines responsible for inhibiting OA-progressive inflammation.[13] When preparing the injection, APS undergoes an additional device centrifugation compared with PRP, to achieve higher concentrations of anti-inflammatory cytokines, growth factors, and leukocytes.[14]

Proposed Mechanism of Action

A key component of APS is maintaining a favourable ratio of pro-inflammatory to anti-inflammatory cytokines, to ensure the harmful effects of pro-inflammatory cytokines are negated.[13] In a study by O'Shaughnessey et al., APS composition from OA patients was compared to baseline levels.[15] The results showed significantly elevated levels of OA inhibiting, anti-inflammatory cytokines such as interleukin (IL)-1ra, soluble tumour necrosis factor receptor 1 (sTNF-RI), and sTNF-RII, along with enrichment in anabolic growth factors.[15] Interestingly, pro-inflammatory cytokine levels were not significantly elevated in the output.[15] It was thought that WBC would have detrimental effects on arthritic joints due to their pro-inflammatory nature, but certain subtypes, such as monocytes and neutrophils,[16,17] produce anti-inflammatory cytokines. Furthermore, a study by King et al. reported a positive correlation between the concentration of WBC and IL-1ra.[13] These findings support the hypothesis that APS formulations with higher WBC levels would be more efficient at reducing inflammation in arthritic joints.

APS injections may promote healing in arthritic joints by influencing macrophage polarization. Macrophages, present in the synovium of arthritic joints,[18] exist in two subtypes: M1 and M2, each having a distinct effect in the joint capsule. M1 macrophages are pro-inflammatory and promote damage within the joint, whereas M2 macrophages release anti-inflammatory cytokines.[19,20] A study performed by Uchiyama et al. examined the effects of PRP and APS injections on macrophage polarization. The study discovered that both solutions contained cytokines involved in macrophage polarization, but APS showed higher concentrations of M1 and M2 related factors. When supernatants were added, both solutions suppressed M1 polarization and promoted M2 polarization. Additionally, PRP and APS stimulated different M2 subtypes: PRP stimulated M2c macrophages, associated with tissue repair, while APS stimulated M2a macrophages, which have anti-inflammatory properties and are associated with wound healing.[18]

The proposed mechanism of APS injections is to suppress degradation pathways and promote anti-inflammation. One key target is the production of matrix metalloproteinase-13 (MMP-13), an enzyme responsible for cartilage matrix degradation.[21] Pro-inflammatory, OA-driving cytokines such as IL-1β and TNFα stimulate chondrocytes to produce MMP-13.[22] In theory, the high ratio of anti-inflammatory to pro-inflammatory cytokines, achieved through the APS system's two device separation and concentration steps, should prevent these cytokines from activating chondrocytes. An in-vitro study by Woodell-May et al. evaluated the effect of APS on MMP-13 levels.[21] The results showed that both anti-inflammatory cytokines, IL-1ra and sTNF-RI, significantly reduced MMP-13 to levels to near-baseline levels.[21] Another study assessed APS's impact on immune cell activity in OA.[23] Using flow cytometry, baseline comparison of the APS output revealed an increase in monocytes, neutrophiles, and T-cells counts and a decrease in the pro-inflammatory B-cell counts. Additionally, APS downregulated genes associated with inflammatory activation and upregulated genes associated with regeneration.[23]

In summary, nSTRIDE APS is an autologous, blood-derived injection that harnesses the patient's own platelets, white blood cells, and anti-inflammatory cytokines to counteract the inflammatory cascade in osteoarthritis. Through a specialized dual-centrifugation process, APS achieves a high concentration of anti-inflammatory mediators—such as IL-1ra and sTNF receptors—while promoting favorable immune responses, including M2 macrophage polarization and suppression of cartilage-degrading enzymes like MMP-13. This unique composition supports inflammation reduction by offering a biologically targeted approach to early OA management.

Clinical Outcomes

Numerous studies have investigated the success of APS, examining pain relief duration, onset time post-injection, and its safety profile.

Several studies have examined the duration and magnitude of pain relief following APS injections predominately in unilateral, primary knee OA patients. In a double-blinded RCT, Kon et al. observed no significant difference between APS and saline control up to 6 months; however, by 12 months, the APS group showed a 65% improvement in WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain scores. The Visual Analog Scale (VAS) for pain showed a 49% improvement in the APS group compared to only 13% in controls.[24] The same study reported that responder rates increased over 12 months, with 65.5% of APS subjects meeting responder criteria on the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) at one year.[24] In a study by Van Drumpt et al., 80% of patients rated themselves as "very much improved" or "much improved" at both 3 and 6 months, while WOMAC functional scores improved by 58.3% and 61% at 18 months.[25] Similarly, Hix et al. reported a 72.5% improvement in WOMAC scores over one year, alongside marked improvements in global impression scores, shifting from "severe" at baseline to "normal, borderline, mild, or moderate" after one year.[26] A long-term follow-up study by Kon et al. in 2020 showed a 50.4% improvement in WOMAC scores at 36 months, with VAS improvements of 31.2%, both notably lower than the 12 month results.[27] Finally, a study demonstrated that 85.7% of patients with an IL-ra:IL-1β ratio greater than 1000 or a WBC count above 30,000/uL, levels, typically achieved with APS injections, met OMERACT-OARSI responder criteria 6 months post-injection.[13] Collectively, these findings suggest that APS injections can provide

	Corticosteroids	Hyaluronic Acid (*HA*)	Platelet-Rich Plasma (*PRP*)	nSTRIDE (*APS*)
Mechanism of Action	Anti-inflammatory and immunosuppressive; inhibits inflammatory cascade	Restores synovial fluid viscosity; provides lubrication and shock absorption	Delivers concentrated anti-inflammatory cytokines and growth factors	High concentrations of anti-inflammatory cytokines, growth factors, and WBCs; suppresses inflammatory pathways and promotes regeneration
Chondroprotection	None; potential for cartilage damage with repeated use	Debated; may have some benefit	Yes; chondroprotective and anti-inflammatory	Yes; targets MMP-13 suppression, macrophage polarization, and inflammatory gene downregulation
Duration of Effect	Short-term (weeks to few months)	Variable; limited duration	Moderate duration; most studies suggest up to 1-year	Longer lasting; benefits often increase over 12 months and can last up to 36 months
Recommended Use	For short-term symptom relief; not for long-term use	Used occasionally; not routinely recommended by AAOS	For mild to moderate OA	For mild to moderate OA
Adverse Effects	Potential joint damage; increased infection risk post-injection	Usually mild; local discomfort	Mild, self-limited	Mild and transient (e.g., joint pain, effusion, nausea); comparable or better than cortisone/HA
Clinical Outcomes	Short-term pain relief, no functional improvement	Mild symptom relief; debated efficacy	Pain relief and functional improvement; depends on OA grade	Substantial and sustained pain and function improvement; better WOMAC/VAS scores in many studies

Table 1. Summary of various options for the treatment of OA; *courtesy of Jihad Abouali, MD, FRCSC.*

substantial and sustained pain relief, often with benefits increasing over the first year.

OA ranges in severity, which has been shown to influence treatment response. This finding was reinforced by a study that assessed pain improvement, based on WOMAC scores, relative to the severity of cartilage damage at the time of injection.[27] The results of this study showed that patients with less baseline cartilage degeneration experienced greater pain relief compared to those with more advanced disease prior to the injection.[27] In 2023, a registry study with 220 knees showed improved knee OA symptoms 1 year post APS injection with the mild to moderate (KL2, KL3) groups showing an increased responder rate compared to knees with more severe OA progression (KL4).[28] These findings suggest that APS injections provide more significant pain improvements in individuals with milder levels of OA compared to those with more severe disease progression.

Safety

Regarding the safety of nSTRIDE, studies have shown very few adverse effects (AE). Van Drumpt et al. and Hix et al. assessed the safety profile of APS injections.[25,26] Van Drumpt et al. reported only mild AEs relating to the device, such as injection site discomfort, injection site joint pain, procedural nausea, and joint effusion, all of which resolved quickly without intervention.[25] Similarly, Hix et al. observed only minor AEs, with one case of arthralgia that resolved within 6 days.[26]

Author's Preferred Approach

In my practice, corticosteroid injections remain a rarely used option due to their short duration of effect and potential for cartilage deterioration with repeated use. While inexpensive and widely accessible, their use is generally reserved for patients presenting with significant inflammation or severe knee osteoarthritis unresponsive to other treatments. The risks of accelerated joint damage and limited long-term benefit warrant cautious application.

Hyaluronic acid (HA) injections have a long-standing safety profile and provide viscoelastic supplementation to the joint, mimicking natural synovial fluid. Despite limited evidence supporting disease-modifying effects and mixed results on symptom relief, I generally reserve HA for patients who have previously experienced good symptomatic benefit or those seeking an option covered by insurance. HA can offer relief lasting up to six months and remains a reasonable choice in these contexts.

Platelet-rich plasma (PRP) injections represent a biologic treatment leveraging autologous blood to concentrate growth factors and anti-inflammatory cytokines. I frequently use PRP for a variety of musculoskeletal and orthopedic conditions, but advise patients that it is not a precise, knee osteoarthritis-specific therapy, given its broad application. Both leukocyte-rich and leukocyte-poor formulations can provide clinical benefit lasting around one year, although cost and lack of insurance coverage remain barriers for some.

For patients seeking a knee osteoarthritis-specific, biologically targeted injection—particularly those who have tried other treatments without success—nSTRIDE Autologous Protein Solution (APS) offers a promising option. APS combines anabolic growth factors with high concentrations of anti-inflammatory cytokines to slow cartilage degradation and counteract the inflammatory cascade in OA. Clinical data support sustained improvements up to 36 months, with a strong safety profile.[25,26,29] While APS may also require out-of-pocket expense, it is uniquely tailored to address primary knee osteoarthritis at a mechanistic level.

Conclusion

nSTRIDE APS represents a promising biologic therapy for the management of knee OA symptoms, with both preclinical and clinical studies demonstrating significant pain reduction and functional improvements. Compared to traditional intra-articular options, nSTRIDE APS appears to offer longer-lasting relief, particularly in patients with mild to moderate disease. Its mechanism of action, targeting inflammatory pathways while promoting chondroprotective effects, aligns with the underlying pathophysiology of OA.[21] Moreover, the safety profile remains favourable, with only mild, transient AEs reported. Taken together, these findings position nSTRIDE APS as a valuable addition to the expanding spectrum of OA management strategies.

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