Reduction in Patellofemoral Bone Marrow Lesions Following Single Arthrosamid Intra -Articular Injection of Polyacrylamide Hydrogel (ipaag) in the Treatment of Advanced Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) of the Patellofemoral Joint (PFJ) manifests as anterior knee pain and impairment of activities that load the PFJ e.g. rising from sitting and squatting [1]. Its significance in OA remains overlooked compared to the Tibiofemoral Joints (TFJ). Osteophytic lesions often manifest first in the PFJ, the presence of which is associated with the progression of structural change in the TFJ [2, 3]. Subsequently, the PFJ accounts for roughly 65% of knee OA, as well as causing greater disability compared to TFJ OA [1]. Yet despite a breadth of treatment options available, PFJ OA remains very difficult to treat [4].

Alternative treatments are thus much needed; one such is the intra-articular injection of polyacrylamide gel (iPAAG). This is a marketed synthetic hydrogel (Arthrosamid®) composed of 97.5% non-pyrogenic water and 2.5% cross-linked polyacrylamide [5, 6]. Polyacrylamide is highly hydrophilic, thus the polymerization of polyacrylamide creates a three-dimensional network that absorbs water, mimicking the natural extracellular matrix. The potential benefits of hydrogels are manifold, including cartilage regeneration, renewal of synovial fluid, and acting as scaffolding for tissue cells, growth factors, and therapeutic drug particles [7].

Both animal and human studies have confirmed the primary mechanism of iPAAG to be the integration of polyacrylamide into the synovial membrane. In doing so it forms a scaffold, facilitating the proliferation of synovial cells and synovial fluid for joint capsule elasticity and viscosupplementation [8-10]. These effects can translate into improved joint mechanics and pain perception, with human studies demonstrating iPAAG to significantly improve joint pain, stiffness, and function for up to 52 weeks [11]. The scaffold may also act as a 'shield' to inflammatory mediators, giving an anti-inflammatory effect on the synovium [6]. iPAAG has also demonstrated the shrinking of intraarticular bony and cartilaginous lesions in goat joints [10]. However, it has not demonstrated any effect on Bone Marrow Lesions (BML) in humans, particularly within the PFJ. We present the first case of a reduction in patellofemoral bone lesions on imaging following a single injection of iPAAG in a patient with knee OA.

Case report

An 81-year-old woman presented to the clinic with anterior knee pain. Further history outlined she mobilized with a walking stick and required assistance to rise from a seated position. To control her pain, the patient was prescribed regular paracetamol and tramadol and took NSAIDs as needed. Scoring tools were used to evaluate her knee pain and severity of knee disability at the time, and are provided in Table 1. A previous knee X-ray had visualized arthritic changes within all three joint compartments: the PFJ, and medial and lateral TFJs. Kellgren-Lawrence scores for PFJ and TFJ changes were reported as grades 4 and 2, respectively.

A knee MRI was done at initial evaluation (Figure 1), confirming osteoarthritic changes, including diffuse subchondral Bone Marrow Lesions (BML) within the articulating surfaces of the femur and patella, as well as the femoral condyles.

After a discussion of treatment options, the patient agreed to opt for iPAAG (Arthrosamid®). A single dose of 6 ml was injected into the knee

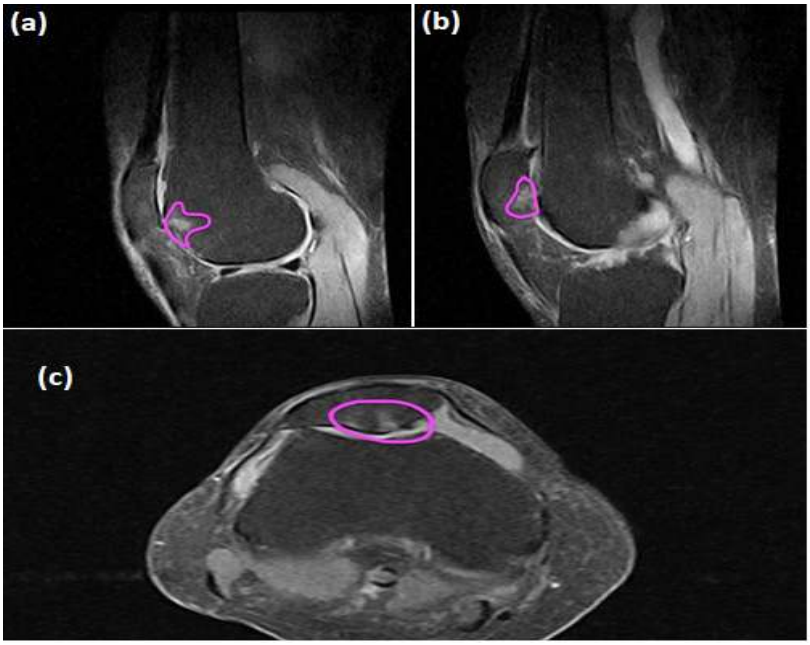

Figure 1. T2-weighted MRI sagittal (a, b), and axial images (c) of the right knee, taken on October 2021, demonstrated bone marrow lesions within the femoral condyle (a), and articulating surface of the patella (b, c); purple outline.

joint under local anesthetic. The injection was carried out on the same day of assessment and was uneventful.

After 4 months, the patient was called for follow-up. On questioning, she reported greater mobility, being able to mobilize without her walking stick, and was able to independently rise from a seated position. Her pain had reduced enough to stop taking paracetamol or tramadol, although she had continued to occasionally take NSAIDs. The same scoring systems at the initial evaluation were repeated, showing marked improvement (Table 1).

Knee MRI was repeated, demonstrating a reduction in the size of the original bone marrow lesions (Figure 2).

Discussion

The patient's symptoms, especially her mobility, greatly improved at follow-up, correlating with a 55% and 136% increase in OKS and LKS, respectively. This is unsurprising considering iPAAG has been demonstrated to improve symptoms within 6 months.6 However, the more important finding was the reduction in the size of BML within the articulating surfaces of the PFJ.

Lesions on both articulating surfaces of the PFJ, so-called 'kissing lesions', are a major burden of arthritic symptoms and are a vital target area in the early management of OA [4]. However, an effective treatment has yet to be demonstrated, primarily due to the unique and distinct biomechanics of the PFJ in comparison to the TFJ [1, 2]. The clear MRI changes seen in this patient are therefore exciting as it suggests iPAAG could revolutionize the treatment of PFJ bone lesions; studies should look towards investigating this on a larger scale.

Other hydrogels that exhibited bone repair required bioactive substrates embedded within the gel, such as cultured progenitor cells or growth factors, and were limited at most to animal models [12]. This is the first injectable hydrogel to demonstrate repair of subchondral bone in humans and without any additional substrates. How this is achieved can only be speculated. The viscosupplementation afforded by iPAAG may protect the articular surfaces of the bones, which could reduce and stabilize OA lesions, as demonstrated previously on MRI of goat joints [10, 13]. Histology of injected goat and horse joints showed the synovial membrane to thicken from the integration of polyacrylamide, but also partially from angiogenesis [9,10,13]. Given that vascularisation is pivotal to bone remodeling this could also explain BML changes [14]. Further investigation is warranted.

The subchondral bone is as equally important as cartilage, with crucial roles in nourishing and maintaining the cartilage, and appropriately distributing force across the osteochondral unit. A systematic review concluded knee BML size correlates with knee pain severity, structural joint progression, and increased risk of knee replacement [14, 15]. The improvements in this patient's pain and functioning could therefore be also explained by the reduction in BML size; the greatest improvements in functioning involved knee extension e.g. rising out of a seated position, and MRI changes were most prominent in the PFJ.

Other treatments, such as zoledronic acid infusion and strontium alienate, have either demonstrated inconsistent effects on BML size and/or knee pain or are limited by their side effects.16 iPAAG can significantly improve symptomatology as aforementioned and possesses an acceptable safety profile [17]. Altogether it offers a potential treatment for bone

Table 1. Showing marked improvement.

Scoring system	Initial evaluation	4-month follow-up
VAS	09-Oct	02-Oct
OKS	27/48	42/48
LKS	33/100	78/100

VAS=Visual analog scale for pain, OKS=Oxford Knee Score, LKS=Lysholm Knee Score. Higher scores on VAS indicate worse pain. Lower scores on OKS and LKS indicate greater knee disability.

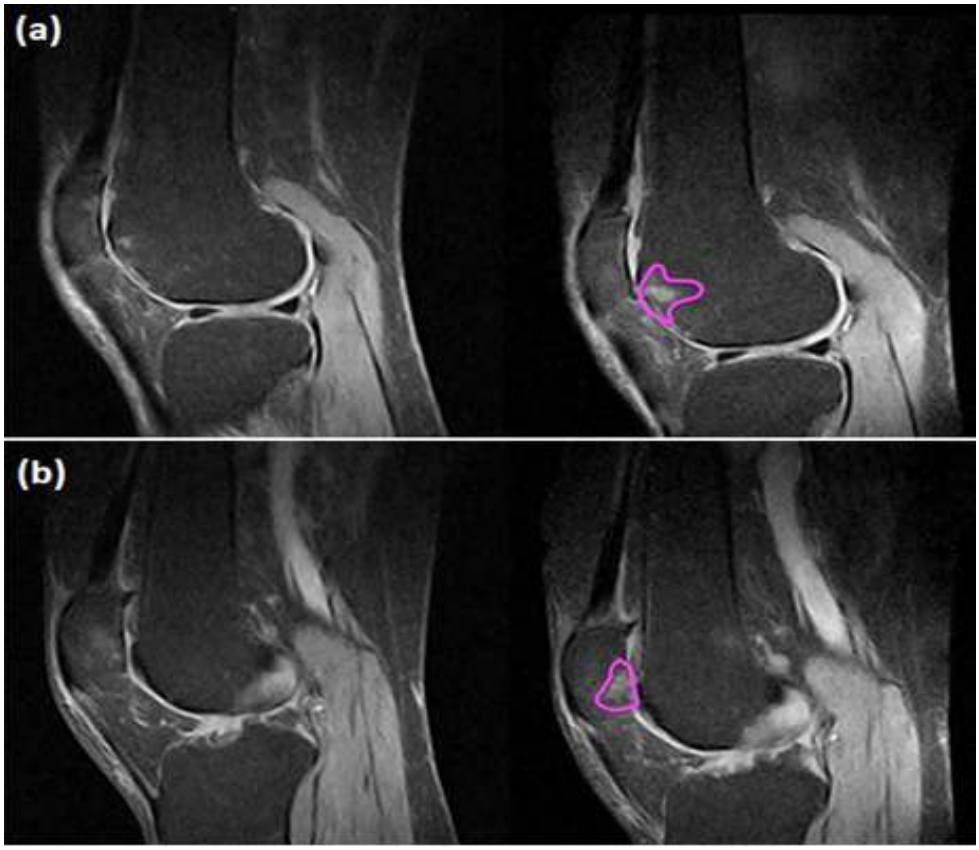

Figure 2. T2-weighted MRI sagittal images of the right knee, taken in February 2022, demonstrated a reduction in the size of bone marrow lesions within the femur (a) and articulating surface of the patella (b). Images on the right are shown again for comparison of size (purple outline).

lesions in OA, with the added advantage of requiring only a single injection. As a non-biodegradable hydrogel, this effect may be long-lasting, however, more long-term follow-up is required to validate this.

Conclusion

This case report highlights two novel applications of iPAAG. It is currently the only injectable hydrogel that can reduce the size of BML in humans, associated with improvements in both joint pain and function, and requires only one injection. Additionally, the findings demonstrate a breakthrough in the treatment of patellofemoral lesions in humans. Larger cohort studies are needed to further evaluate these effects, with longer follow-up to establish the longevity of bone changes.

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