SPECIAL COMMUNICATION

Percutaneous Management of Osteoarthritis in the Knee: Proceedings from the Society of Interventional Radiology Research Consensus Panel

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ABBREVIATIONS

GAE = genicular artery embolization, GNA = genicular nerve ablation, NSAIDs = nonsteroidal anti-inflammatory drugs, OA = osteoarthritis, RCP = research consensus panel, SIR = Society of Interventional Radiology, TKA = total knee arthroplasty

BACKGROUND

Osteoarthritis (OA) of the knee is a complex, multifactorial disease with no known cure (1). Treatment options seek to manage symptoms, since no proven disease modifying therapies currently exist. However, for several patients, adequate and sustained symptom control can be challenging to achieve. Depending on disease severity, various

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treatments for osteoarthritic knee pain are available, ranging from physiotherapy/diet modification to total knee arthroplasty (2). As no single modality has been shown to be completely effective, the treatment frequently involves a combination of pharmacologic therapies and non-pharmacologic interventions with joint replacement reserved for those with severe joint disease, pain, and functional limitations (3).

Minimally invasive methods to treat knee OA have recently emerged as an alternative or adjunct to conventional nonsurgical treatments. These image-guided procedures, genicular artery embolization (GAE) and genicular nerve ablation (GNA), demonstrate promise as minimally invasive methods to reduce arthritic pain and dysfunction caused by knee OA (4,5). Given the relative novelty of these procedures and paucity of high-level data supporting their routine use, the Society of Interventional Radiology (SIR) Foundation gathered a multidisciplinary group of experts to form a research consensus panel (RCP) to further explore the key questions, gaps in literature, and priorities for future research surrounding the percutaneous management of knee OA.

METHODS

Panel Membership

On January 28, 2021, SIR Foundation convened an RCP for the development of a research agenda on the percutaneous management of knee OA. The panel was composed of a multidisciplinary group of experts from orthopedic surgery, rheumatology, anesthesiology/pain management, sports medicine, and interventional radiology. There were 13 expert panelists, including 9 interventional radiologists and 1 from each of the other specialties. An audience comprised of invited interventional radiologists, a member of the SIR Comparative Effectiveness committee, and related industry partners were also present.

Agenda Methodology

The goal of the RCP was to provide a summary of the existing knowledge, identify current gaps in the literature, and prioritize research needs for the percutaneous management of knee OA. In addition, the panelists were asked to identify the critical relationships/alliances that should be developed and fostered to advance the prioritized research and determine how SIR and the SIR Foundation can further support these initiatives.

Ten panelists produced a 10-minute presentation in their area of expertise. Within each presentation, the panelists were asked to lay the groundwork of current knowledge in their area of expertise, define the outstanding gaps in knowledge that could be reasonably addressed with a clinical trial or registry, describe future directions that merit investigation, and suggest guidance as to how interventional radiologists could become engaged in these research efforts. The critical question that evolved in this RCP was the mechanisms needed to validate GAE/GNA as accepted treatments within guidelines for knee OA along with establishing reimbursement pathways for GAE. Following the panel led presentations, round table discussions were held to elaborate gaps in knowledge, evaluate subsequent research questions, and explore strategies to answer the research needs. Furthermore, the audience was engaged in the discussions. Lastly, research ideas were prioritized.

RESULTS

The panelists offered 10 presentations, the results of which are summarized as follows.

Scope of the Problem and Pathophysiology

The global burden of disease study conducted by the Institute of Health Metrics and Evaluation estimated the prevalence of hip and knee OA to be 303.1 million, representing an approximately 9.3% increase between 1990 and 2017 (6). Within the United States, Deshpande et al estimated that 15.1 million individuals had symptomatic knee OA in 2012, which constituted 6.9% of the total population over the age of 25 (7). The study also concluded that knee OA affects not just older adults, but also millions of younger and middle-aged adults, with a large portion of this afflicted population having to live with symptomatic knee OA for the majority of their lives (7).

While OA has historically been described as a "wear and tear" disease, leading to loss of articular cartilage; newer studies now consider inflammation as a driver of the OA process with synovitis representing a critical feature (8). This inflammatory process may promote synovial angiogenesis that is accompanied by nonmyelinated sensory nerve growth into the joint (9–11). This process may contribute to pain in OA as normally aneural structures (ie, articular cartilage and inner two thirds of the meniscus) are now exposed to chemical and mechanical stimulation (9). Synovial neovascularity can also contribute to structural progression and tissue differentiation. Therefore, inhibiting angiogenesis may reduce the ossification of osteophytes and the deep layers of articular cartilage. The anti-inflammatory effects of angiogenesis inhibition may also slow the progression of joint damage in patients with the disease (9).

Surgical Therapy for Knee OA

Knee OA can be divided into 2 categories. The first category is global degenerative OA, which is characterized by osteophyte formation, subchondral cysts, joint space narrowing, and loss of articular cartilage. The other category is focal articular cartilage defects, which can occur in isolation or with underlying degenerative changes. Whether an isolated lesion or a global degenerative change occurs, articular

cartilage lesions are difficult to treat surgically because they are primarily avascular, aneural, and have a limited regenerative potential.

Surgical treatment is typically indicated when conservative measures have failed. These options can range from knee arthroscopy to partial and total knee arthroplasty. Arthroscopic interventions may include joint lavage, meniscal and cartilage debridement, removal of loose bodies, partial meniscectomy, and restoration of isolated cartilage lesions with cellular therapy. Osteotomy and abrasion arthroplasty (ie, microfracture) also represent options for the treatment of malalignment and focal articular cartilage defects, respectively. Primary goals for surgical intervention are to relieve pain, swelling, mechanical symptoms of catching, locking or giving way, and returning patients to their sport or activities of daily living. However, the current evidence for these less invasive surgical treatments is limited (12–16). Presently, arthroscopic interventions for knee OA with mechanical symptoms require careful patient selection, specific goals for the surgical intervention, and patient education with appropriate expectations discussed to optimize outcomes and patient satisfaction. Further, the limited evidence to support the long-term efficacy of these surgical options has led to an expansion of studies evaluating alternative non-arthroplasty treatment options.

Rheumatology Perspective

OA is initially treated with nonpharmacologic approaches, such as exercise and periarticular musculature strengthening (17). Despite the advantages of nonpharmacologic therapy, most patients will eventually require medications to control their OA pain. Rheumatology guidelines strongly recommend the use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for knee OA, based on evidence that topical NSAIDs are superior to placebo for up to 12 weeks (3,18,19). Moreover, oral NSAIDs remain as the most significant class of therapy for those who can tolerate them and may yield sustained pain palliation for several years. Minimally invasive techniques, including the injection of intra-articular glucocorticoids, can also be used for short-term pain palliation as relief is not long-lasting (20). Other techniques aimed at interfering with nociceptive transmission from the knee capsule have been explored via cryoneurolysis, GNA, and more recently, GAE. At present, there is insufficient evidence to confirm these as safe and effective treatments, with discordant recommendations among rheumatologic guidelines (3,18). One major difficulty in the validation of novel OA treatments is that OA pain, in general, is highly susceptible to the placebo effect (ie, >40%); therefore, all interventions may be expected to see substantial pain responses to placebo (21). In addition, the effect size of placebo increases as the intervention under evaluation has an increasing invasiveness (22). For this reason, it is imperative that blinded trials with appropriate comparators (preferably placebo) be performed to establish benefit from these procedures and mitigate or eliminate the risk of a placebo effect.

Nonsurgical Management Overview

Nonsurgical treatments can be further divided into non-interventional and interventional procedures. Non-interventional procedures include physical therapy, braces, and aquatherapy. Interventional treatments that are widely used include GNA and intra-articular injections with corticosteroids, hyaluronic acid, platelet-rich plasma, or stem cells (23). Intra-articular glucocorticoid injections are among the most utilized interventional treatments, although may contribute to the progression of radiographic arthritic changes in the treated knee compared with more conservative regimens. Major side effects may also occur, including skin depigmentation, fat, skin or muscle atrophy, adrenal insufficiency, hyperglycemia, and septic joint (24). Hyaluronic acid injections are an alternative to glucocorticoids and can be used every 6–12 months, although pain relief provided has not been reported to be superior, and several insurance carriers are no longer covering hyaluronic acid injections (25).

Biological Therapies

Recent advances in cellular-based therapies suggest these may represent a promising treatment option to fill the treatment gap for patients with knee OA uncontrolled by conventional medical therapies that are ineligible for joint replacement. Orthobiologic injections, which include mesenchymal stem cells, have recently been applied for the treatment of OA. The most common sources for mesenchymal stem cells include bone marrow and adipose tissue given the ease of accessibility, although several birth tissue products, such as amniotic and placenta-derived cells, are also marketed for use in this field. However, there is a common belief that orthobiologic injections are unproven or unsafe for current use in orthopedic conditions. While there are not several randomized controlled trials evaluating their efficacy, their safety has been well established with a large multicenter prospective analysis demonstrating no increased risk of neoplasm or other major adverse events (26–28).

GNA (Anatomy and Mechanism of Effect)

Standard targets for GNA involve the superior lateral, superior medial, and inferior medial genicular nerves. The recurrent peroneal nerve innervates the inferolateral knee capsule, but is close in proximity to the main peroneal nerve and has therefore not been targeted in any GNA study to date (29). Successful neurolysis via radiofrequency ablation involves a complete nerve disruption. Partial neurolysis may lead to increased pain among patients. Frictional heating to at least 40–50°C is required for the destruction of the soma/ganglion or axon/nerve (30). The anatomic literature lacks consensus on the specific number and origin of afferent

Table 1. Research Questions

- What would be the ideal trial design for a randomized controlled trial of GAE or GNA?
- Is a large scale, multicenter sham study feasible?
- Are there ethical implications of a sham study for an intervention, such as GAE, due to the risks of angiography?
- Would an alternative comparator to a sham treatment be acceptable?
- What is the ideal patient population for investigation in GAE?
- How can we standardize and optimize the technique for both GNA and GAE?
- What is the comparative efficacy of GNA to GAE?
- What are the ideal and objective outcome measures for measuring functional response to OA therapies?
- What is the angiographic appearance of the knee following nerve ablation (ie, does concurrent arterial injury occur?)
- What is the impact on proprioception to the knee following GNA?
- Does GAE impair wound healing or otherwise negatively impact patients with OA who choose to undergo total knee arthroplasty?
- What evidence is needed to support reimbursement for GAE by commercial third-party payors?

GAE = genicular artery embolization, GNA = genicular nerve ablation.

nociceptive neural pathways from the knee joint capsule. However, there is consensus that the branches of the femoral, sciatic, and obturator nerves are involved. Some variations in the precise course of the nerves exist based on studies involving cadaveric dissection. This feature provides rationale for why spherical ablation zones with 10–12-mm diameter may improve outcomes in patients and prevent partial neurotomy.

GNA (Current Clinical Evidence)

The current evidence suggests durable improvement in chronic knee pain after GNA when compared with conservative therapy or intra-articular injections with glucocorticoids or hyaluronic acid derivatives (31–34). A prospective, multicenter, randomized trial by Davis et al compared long-term clinical safety and effectiveness of GNA with intra-articular steroid injections. The study included 151 patients with chronic (≥6 months) knee pain who were unresponsive to conservative modalities. The study concluded that patients who underwent GNA reported significantly better reduction in pain and medication use (32). Additionally, Choi et al compared GNA with a sham procedure in 38 patients, finding that visual analog score and Oxford knee scores were significantly lower following GNA at 4 and 12 weeks after the procedure, and the majority of patients reached at least 50% knee pain relief at follow-up (35).

GAE (Anatomy and Mechanism of Effect)

GAE attempts to target and inhibit angiogenesis that occurs from the proinflammatory state in knee OA. To achieve this, there are 6 vessels that are typically targeted during GAE, which include the medial superior genicular artery, medial inferior genicular artery, lateral superior genicular artery, lateral inferior genicular artery, descending genicular artery, and anterior tibial recurrent artery (36–39). Studies have demonstrated that all 6 arteries are present in most patients, with asymmetry in size between vessels and collateralization of supply across the joint being both been reported (36–38). The specific mechanism of action of GAE is to arrest the downstream effects of inflammation, which include the growth of unmyelinated sensory nerves in the articular and periarticular structures and the release of cytokine/neuropeptides that exaggerate response to pain stimuli. Further, GAE may halt synovitis that is suspected to cause the progression of articular cartilage loss in knee OA. In this manner, GAE may additionally confer protection to the osteochondral surface in patients and modify disease progression (40).

GAE (Current Clinical Evidence)

The limited published data available suggests that GAE is effective in reducing knee pain from OA (36,37,41–43). These studies include single-arm prospective trials, a retrospective case series, and a systematic review. The largest study to date, by Okuno et al, described GAE for mild to moderate knee OA in 72 patients primarily using a solution of imipenem/cilastatin (36). Eighty six percent of these patients met the primary endpoint of a 50% decrease in the Western Ontario and McMaster Osteoarthritis Index pain score at 6 months. Bagla et al performed a prospective, 2-site pilot study that included 20 patients with mild to moderate OA using 75- or 100-micron-sized microspheres (37). The global Western Ontario and McMaster Osteoarthritis Index score was reduced from 61 at baseline to 31 at 6 months. Complications included self-limiting skin discoloration without ulceration (13/20) and transient plantar numbness (2/20) after GAE. Additional GAE trials are underway, including a randomized controlled trial comparing GAE with a sham procedure.

Who Goes Where? Treatment Prioritization for Knee OA

The treatment of knee OA is a holistic process with a shared decision component that is individualized to each patient. An individualized treatment plan implies that monotherapy may be appropriate for some patients; alternatively, for others a combination of therapies may be needed (18). Furthermore, psychosocial factors are frequently accounted for. These measures include those aimed at improving mood and reducing stress along with the core fundamental strategies of exercise and weight loss (3). Disparities in access to care and

Table 2. Proposed Research Topics (Ranking of Priorities)

1.	Subject minimally invasive options to rigorous prospective multi-arm investigation, to include analysis for optimized patient selection.
2.	Evaluate/document real-world outcomes of minimally invasive procedures to manage knee OA.
3.	Evaluate the safety/efficacy of radiofrequency ablation in the management of knee OA.
4.	Assess if GAE precludes or complicates subsequent TKR.
5.	Investigate if the failed TKA represents the ideal patient group for targeting with GAE and/or GNA.
6.	Evaluate GAE versus GNA in the setting of painful knee OA.
7.	Technique standardization for different modalities.
8.	Identify risk factors for failure following GAE or GNA in patients with advanced knee OA.
9.	Evaluate the safety/efficacy of cryoneurolysis in the management of knee OA.
10.	Investigate if GNA nonresponders are the best (or ideal) patient group to target for GAE.
11.	Evaluate the cellular effects of GAE.

GAE = genicular artery embolization; GNA = genicular nerve ablation; OA = osteoarthritis; TKA = total knee arthroplasty; TKR = total knee replacement.

cost of interventions may also play a role in treatment selection.

Pharmacologic therapies should be implemented with the strategy of using treatments with the lowest amount of systemic exposure or toxicity. Local therapies, such as topical NSAIDs, are therefore performed as initial treatments. Systemic agents, such as oral NSAIDs, are applied with the intention of providing short-term pain relief. Present guidelines from the American College of Rheumatology do not support the use of intra-articular stem cell or platelet-rich plasma treatment due to heterogeneity in preparation and the lack of technique standardization (18).

GNA may play a role in the present management of patients with knee OA with pain refractory to conventional pharmacologic and nonpharmacologic treatments given its advantages as a local, minimally invasive therapy that may reduce the utilization of narcotic medications (18,35). GNA and GAE will require similar safety and efficacy data to confirm their role in the algorithm for management.

PANEL DISCUSSION

Following the presentations, the panelists identified the current gaps in knowledge (**Table 1**). Subsequently, a list of research ideas was proposed and prioritized using a weighted ranking system (ForceRank) (**Table 2**). The panel acknowledged that conducting a randomized controlled trial that seeks to establish the safety and efficacy of percutaneous treatments for knee OA was the top priority of this RCP. It was discussed that a trial of this magnitude may lead to the incorporation of GNA/GAE into societal guidelines for OA management and would also provide interventional radiologists the evidence needed to safely offer these procedures to patients directly. Furthermore, it was decided that this data could offer justification to achieve reimbursement and on-label microsphere indication for GAE, since widespread utilization and subsequent clinical research or registry data would otherwise be curbed without it.

With respect to trial design, there was debate about the ideal comparator arm, with the panel reaching consensus that a sham treatment represents the gold standard given the high placebo effect (>40%) seen with past OA studies. However, there was a notable concern that a sham study would present challenges to implement from a practical and ethical standpoint, as the risks of angiography are not trivial, and obtaining an institutional review board approval consequently may not be feasible. Comparisons to the standard of care treatments, such as NSAIDs or intra-articular glucocorticoid injections, were determined to be logistically simpler, although trials with this design make proving superiority of the experimental treatment more difficult. Optimal patient cohorts for evaluation were also discussed, with potential groups, including patients who failed total knee arthroplasty (TKA) or a pre-surgical cohort ineffectively managed by medical therapies, but ineligible for or not desiring surgery. The failed TKA group, defined as persistent chronic knee pain, was initially believed to be advantageous given a regret rate following TKA of 19% or up to 500,000 patients annually with no known effective treatment options. At the end, the panel concluded that a pre-surgical cohort was more appealing given a similar need and market for effective therapies but greater potential for demonstrating the efficacy of percutaneous therapies due to the lower baseline severity of arthritic disease.

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