PANEL DISCUSSION

Optimizing MSK Embolization Research and Adoption

Reviewing the current state of MSK data and applications and looking ahead to predictions, potential developments, and getting support from the OA community.

With Yuji Okuno, MD; Gerard Goh, MD; and Matthew J. Scheidt, MD

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What are the most promising or interesting applications currently being explored in musculoskeletal (MSK) embolization research?

Dr. Okuno: Sports injury followed by knee osteoarthritis (OA) and frozen shoulder.

Dr. Goh: Genicular artery embolization (GAE) for OA is probably the most researched area in MSK embolization at the moment. We are seeing many different trials being conducted around the world, and it is interesting to see that many now-published studies are demonstrating promising early favorable outcomes.

As MSK embolization has a wide range of possible applications, it is interesting to see numerous studies in different spaces. Research is being conducted in tenosynovitis, chronic synovitis, plantar fasciitis, postoperative pain control, frozen shoulder, and even cutaneous pain syndromes. It is a rapidly growing and exciting space.

Dr. Scheidt: Starting with the most promising areas of exploration in MSK embolization, GAE appears to demonstrate the earliest positive results for patients. Several systematic reviews and meta-analyses have demonstrated clear improvement in visual analog scale and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for patients who have undergone GAE, and the benefits appear to be sustainable out to 2 years. Other areas of investigation that are lacking much more than safety and feasibility data are embolization treatment for adhesive capsulitis, patellar tendonitis, plantar fasciitis, epicondylitis, and other MSK inflammatory ailments.

In addition, I think we are only in the early stages of understanding how embolization can be used for MSK oncologic treatment, namely desmoid tumors (DT) and sarcomas. Drug-eluting bead transarterial chemoembolization (DEB-TACE) has been studied in phase 1 studies and shown to be safe and effective as a local treatment alternative for DT.

In which applications are the existing data support strongest?

Dr. Okuno: Knee OA; however, when considering the aspect of comparison with other treatments, sports injury will potentially have a strong and unique position.

Dr. Scheidt: As of today, the strongest supporting data exist in GAE for nonsurgical candidates with OA. Several phase 1 studies have been pooled, as previously mentioned, in meta-analyses demonstrating promising efficacy in regard to pain scores and function. These data are also backed up by a single, randomized, sham-controlled study demonstrating no improvement in the sham group and significantly greater pain reduction in the treatment arm.[1]

Dr. Goh: The data are strongest in embolization for knee OA. Since the landmark paper by Dr. Okuno and colleagues,[2] we have seen trials being published for OA, including many randomized controlled trials. We can also draw some information from the existing studies going back many years that examined embolization for hemarthrosis.

What are the unique challenges in evaluating MSK techniques and outcomes (ie, unique vs other indications)?

Dr. Scheidt: Any time you are talking about treatment for MSK ailments where the main outcome is pain reduction, there is a concern for placebo effect when assessing pain response. These issues can be mitigated by using more vetted assessment tools, such as WOMAC and Knee Injury and Osteoarthritis Outcome Score for patients with OA.

MSK embolization has its own unique challenges in regard to technique because, unlike what we often see with solid organ tumor embolization, the site of treatment is generally not supplied by a single arterial supply. The regional anatomy and target vascular supply can vary significantly between patients, thus limiting widespread adoption of these treatments among endovascular specialists. In addition, there is not currently a consensus on the most appropriate embolic material to use for MSK embolization procedures, which limits comparison of results across studies.

Dr. Okuno: What is unique about the field of MSK embolization is that the endpoint is a subjective measure: pain. We believe that objective data, such as how quickly the patient can walk, how much function has been restored, and how much the imaging findings have improved, should also be evaluated.

Which characteristics are most important with respect to embolic materials in MSK applications? Does this vary based on the target anatomy (ie, knee vs shoulder)?

Dr. Okuno: Safety is very important because the patient population will be relatively healthy. Important aspects of safety (ie, side effects) include skin damage, peripheral nerve damage, and posttreatment pain.

The properties of the ideal embolization material vary depending on the site. For example, there are data showing that the permanent sphere–type embolic material fits in knee OA but not in the shoulder. We speculate that there are structural differences in the target vessels.

Dr. Goh: With many MSK embolization applications, it is impossible to be absolutely selective of only the arteries to the target area. More often than not, small nontarget arteries will be embolized. For this reason, there is a school of thought that biodegradable embolic materials are preferred over permanent embolics. Permanent embolics may cause longer-term tissue ischemia and infarction to nontarget areas but also may cause infarction to the area of interest. Whether this affects longer-term tissue viability or influences functionality is yet to be determined.

Dr. Scheidt: The degree to which the material penetrates the area of interest. Smaller particles will inherently cause greater ischemic changes and possibly cause infarction of adjacent structures (eg, bone). If the material penetrates too deep, it can cause ischemic injury to the skin as well, which we have seen with smaller particle use in GAE.

In addition, as with any minimally invasive, endovascular treatment, the time required to perform the procedure also matters. The ideal embolic material allows for efficient delivery of the material to achieve an adequate endpoint in the target vessels while limiting nontarget embolization. Reducing physician and patient procedural time are extremely important as we move forward with different soft tissue embolization procedures.

What is the status as to development and trials of indication-specific materials?

Dr. Goh: As there are many different kinds of embolic agents available, we are not unsurprisingly seeing many different embolics being used for MSK embolization. The main embolics being used are particulate embolics, such as polyvinyl alcohol particles and crystalline imipenem. Many trials and studies are evaluating different embolic agents,

with some comparative trials between agents. Of interest is the development of specific biodegradable embolic agents for MSK embolization. Work on developing these temporary embolic agents that degrade at specific time points, so as not to cause infarction, is being undertaken.

Dr. Okuno: To improve the safety and efficacy of embolization, we are developing a temporary embolic particle—a quick-resolvable gelatin particle that dissolves in 2 to 4 hours. We have developed two types, a spherical type for the elbow and knee and a sponge type for the shoulder. Different properties are needed for the elbow, knee, and shoulder, and we developed them to adapt to each. More than 150 cases have been treated with each developed particle, and the data show increased safety compared to permanent embolic particles.

In terms of convincing the OA community, what kinds of trials and outcome data will be most compelling?

Dr. Scheidt: Clearly, we need to move beyond phase 1 safety and feasibility studies and begin focusing efforts on comparative, randomized controlled trials. Comparing currently available and accepted treatment options used for pain control of a multitude of inflammatory MSK conditions with MSK embolization treatment paradigms will help demonstrate noninferiority and potentially more significant reduction in subjective pain response and functional outcomes. Two components that must be more intensely explored prior to widespread adaptation of GAE for OA are (1) cost-effectiveness of the treatment versus alternative commercially available options and (2) continued understanding of the underlying pathophysiology of the treatment effect. It is imperative to demonstrate how embolization elicits the positive effects on patients before referring physicians will accept embolization as a viable treatment option.

Dr. Okuno: We need: (1) a durability study to determine how long a patient can maintain the effect of the treatment once improved; (2) a comparison study with other treatments (steroid injection, hyaluronic acid injection); (3) comparison of patients who underwent immediate surgery for severe OA and those who underwent conservative and minimally invasive treatment in combination with GAE, nerve ablation, etc; and (4) a study on the effectiveness of GAE for patients with persistent pain after total knee arthroplasty surgery.

Dr. Goh: As with many endovascular trials, patient numbers are a challenge when comparing against other therapies, such as drugs. Drug trials, particularly for a common condition such as OA, often have thousands and sometimes tens of thousands of patients. A well-designed trial with a robust patient selection that examines the commonly used OA outcome scores (eg, WOMAC in GAE) as well as safety is important. Like many novel procedures, one temptation is to design trials that are more inclusive to boost numbers but at the detriment of being less rigorous in patient selection, which could lead to poor study results.

When you see patients for consultations, what are their most common questions and concerns, and how do you address them? What outcomes are most important to them?

Dr. Okuno: First is safety data—what side effects are possible, as well as the extent and expected duration. With permanent embolic substances, skin damage occurs in about 15% of cases, almost all of them mild. Neuropathy occurs in about 10% of cases and is mild and improves in 2 to 4 weeks. Posttreatment pain is present in most patients but lasts only a few days. Use of a temporary embolic particle can reduce the frequency and extent of the above.

Second is short-term effectiveness data—the percentage of people who have received treatment and have benefited from it. Seventy-five percent of patients with knee OA say they are clearly better than before, and this percentage remains almost the same or decreases to 70% after 1 year. Short-term results also depend on the results of the pretreatment MRI. Results are limited when severe bone marrow damage, severe cartilage loss, or severe meniscus tear are present.

Dr. Scheidt: The most common question that patients want answered is, "Will this work?" We anecdotally know that some patients experience significant pain relief but are unable to definitively say whether it will work better than other available treatment options. The second most common question in consultation is, "Will insurance cover it?" In today's ever-changing health care environment, there is no way to know for certain, but we start the preapproval process as soon as possible after the consultation to help patients make an informed decision on whether to proceed.

Regarding outcomes, patients are most concerned about pain reduction and treatment durability. There are limited data on the latter, and I simply remind them that although we do not have those answers currently, it will not limit their eligibility for any other available treatment options in the future, including surgical joint replacement.

What are your predictions for the near future of MSK embolization?

Dr. Goh: This is an exciting area that will continue to grow, with many different possible applications. I predict GAE for OA will gather more momentum as more evidence is generated. Embolization for other applications within MSK (eg, chronic synovitis/tenosynovitis, plantar

fasciitis) holds promise, and it will be exciting to see evidence being generated for these.

Dr. Scheidt: I think we may see several randomized comparative studies exploring the use of embolization for treatment of a variety of MSK inflammatory ailments. These studies will add to the existing safety and feasibility studies that are currently available, hopefully proving the efficacy of embolic treatment for a variety of conditions.

In addition, we have only scratched the surface on use of embolization as a local treatment alternative for soft tissue tumors, and I am excited to see where this leads in the next several years. Although these procedures can be technically challenging, intuitively there is reason to believe that hypervascular tumors located in bone and soft tissue would respond to bland embolization, TACE, or DEB-TACE in a similar fashion to tumors located elsewhere, such as the liver. Extrapolating historical data on embolic therapies targeting solid-organ hypervascular tumors, I think we may see an expanded role for endovascular treatment in the MSK oncology space.

Dr. Okuno: Since only permanent embolic material is currently available, these embolic substances will be used for some time to come; however, temporary embolic material will gradually become the preferred embolization material for safety reasons. Currently, GAE is the most commonly performed procedure (because of the permanent spherical fit to GAE), but as temporary embolic material is developed and distributed, cases of sports injury and frozen shoulder will increase.

In the future, embolic substances will be developed that can be safely used for low back pain and neck pain, and these will also become important indications. Embolization of pelvic inflammation, such as prostatitis, will also become more widespread. ■

Disclosures
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