Pharmaceuticals for Intra-arterial Therapy

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ABSTRACT

Clinical pharmacology may be defined as the branch of medicine concerned with the therapeutic agents used in the prevention, treatment, and control of disease. Pharmaceuticals are the specific agents used to combat disease. Hence, many of the agents used by the interventionalist may be considered pharmaceuticals. Safe and effective use of these therapeutics requires understanding of vascular anatomy and disease pathology, proper technique, and knowledge of the therapeutic agents. This article reviews many of the agents available and some that are on the horizon. The future of transarterial therapies is bright and holds many promises.

KEYWORDS: Intra-arterial therapy, embolization, pharmembolics, pharmaceuticals, cellular transplantation

Objectives: Upon completion of this article, the reader will understand the common mechanical and biologically active embolic agents and the application of these agents in vascular and nonvascular disease.

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Stedman's dictionary¹ defines clinical pharmacology as the branch of medicine concerned with the therapeutic agents used in the prevention, treatment, and control of disease. Pharmaceuticals are the specific agents used to combat disease, and therefore much of what an interventional radiologist injects through a catheter can be considered a pharmaceutical. This article is organized into embolic and nonembolic therapeutics. Embolics can be further classified as either large or small. Pharmaceuticals can be further differentiated according to mechanism of action, being based on either biological or mechanical properties.

Vascular embolization was first attempted at the beginning of the 20th century.² Since then, sophisticated

tools, techniques, and agents have been developed for transarterial therapy. The primary goal of the early agents was to stop bleeding and ablate targeted tissue and vascular malformations. Their mode of action was mechanical occlusion of blood vessels. The next generation of intra-arterial therapeutics relied on the targeted delivery of chemicals, radiation, biological agents, or heat to accomplish tissue ablation, possibly with greater effect.³

Safe and effective use of these therapeutics requires the proper technique, an understanding of the vascular anatomy and pathology being treated, and knowledge of the delivery system and the agents used. The choice of the agent depends on the target organ, the

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Table 1 Materials Commonly Used for Transarterial Therapy

Therapeutics	Size
<i>Permanent Materials</i>	
Large embolics	
Coils	Multiple
Biologically modified coils (coated with biologically active substance or embedded cells)	
Particles	
Polyvinyl alcohol particles (amorphous)	45–1180 μm
Spherical embolics	
Spherical PVA, Bead Block, Embospheres	40–1200 μm
Pharmaceutical embolics (pharmembolics)	40–500 μm
Available or in trials	
SIR-Spheres [®]	
TheraSphere [®]	
Islet cells	
Other agents “on the horizon”	
Dox-Spheres	
Thermo-Spheres	
Orphan or promising technology	
MTC-Dox spheres	
<i>Liquid Agents</i>	
Commonly used	
Ethanol (dehydrated)	
Iodized oil (Ethiodol, Lipiodol)	
Glue (<i>n</i> -butyl cyanoacrylate (<i>n</i> -BCA))	
<i>Biodegradable Materials</i>	
Gelatin sponge (Gelfoam or Surgifoam)	40 μm –4 mm
Microfibrillar collagen (Avitene)	5 μm $\times$ 70 μm
Collagen sponge (Ultrafoam TM)	
Starch microspheres (Spherex)	20–100 μm
PVA, polyvinyl alcohol.	

disease process being treated, and the goal of the therapy. Mechanical devices such as coils or balloons are needed to occlude large vessels. On the other hand, particulate agents are needed to occlude higher order branches to capillaries and perform tissue ablation. Sometimes, however, mechanical occlusion is not required to achieve the therapeutic goal. Liquid agents (e.g., dehydrated alcohol) may be used to cause coagulative necrosis of tumors or organs. Some of the commonly used materials are listed in Table 1.

Ideally, a therapeutic agent that is administered intra-arterially would have the following characteristics: (1) predictable sizing, flow, and phase behavior; (2) nonclumping (to improve delivery and to prevent occlusion of catheter); (3) temporarily radiopaque (to allow artifact-free imaging in the future); (4) systemically nontoxic but toxic to targeted tissue when desired; (5) ability to elute a drug or deliver radiation and biological agents at a particular rate; (6) nonallergenic; and (7)

affordable. Its design should allow easy and controlled delivery to the target territory through microcatheters or conventional catheters. It should provide reliable tissue ablation mechanically or with attached therapeutics. The clinical scenario should help guide the interventionalist to choose the appropriate agent (Table 1).³

LARGE EMBOLIC AGENTS

Large embolic agents are designed to occlude vessels ranging from 1 mm to several millimeters in diameter. Such embolics include microcoils (0.018 inch), larger coils (0.035, 0.038, and 0.052 inch), detachable balloons, and gelatin sponge “torpedoes.”

Mechanical Embolic Agents

Coils are an example of a therapeutic agent with a mode of operation based primarily on mechanical obstruction. The coil embolics are made from platinum or stainless steel. Most are covered with Dacron fiber to promote thrombosis. After delivery, coils can either be pushed free from a catheter using a wire, with a forceful injection, or be detached by electrical or mechanical detachment systems to allow more controlled release. Hydrogel-coated coils that have a small diameter during placement but are able to absorb fluid and expand to fill a much greater volume are now available.

These larger embolics work primarily by causing an endovascular “ligation” of blood vessels. Examples of their uses include (but not limited to) occlusion of the gonadal veins in a patient with a varicocele, proximal occlusion of a common iliac artery or internal iliac artery prior to endovascular repair of abdominal aortic aneurysm, and occlusion of a focal bleeding site or pseudoaneurysm. The advantages of these devices include precise placement and minimal damage to the surrounding vascular supply (when used in an artery). Similarly, detachable balloons provide precise control and large vessel occlusion.

The use of coils and balloons results in a permanent vascular occlusion. Sometimes, however, temporary occlusion of an artery is indicated. Temporary occlusion of arteries that are 2 to 4 mm in diameter may be performed with gelatin foam torpedoes (off-label use but within the standard of care). These torpedoes are shaped by cutting 2 mm wide (at the base) by 10 mm triangles or strips and rolling them into a cone or cigar shape. The torpedo is then back-loaded into the tip of a 1-mL syringe filled with dilute contrast material (Fig. 1). Under fluoroscopic guidance, it is then injected slowly into the target vessel. To avoid reflux into a nontarget vessel, the catheter should be well seated but not wedged into the artery.^{3,4} Delivery of torpedoes results in an immediate but temporary vascular occlusion as the gelatin sponge is resorbed.

Figure 1 (A) A sheet of gelatin sponge (Surgifoam). To form a slurry mixture, it can be cut in 1- to 2-mm pieces and used with a setup similar to the syringe-stopcock apparatus shown. One syringe may be filled with the pieces and the other with dilute contrast material. With the stopcock open to both syringes or partially closed, back-and-forth agitation helps to macerate and suspend the gelatin foam pieces in the dilute contrast material to form the slurry mixture (not shown). (B) How gelatin foam strips and triangles may be formed into torpedoes and a 1-mL syringe loaded with a torpedo. (C) A magnified view. Although here the tip is shown to be outside the tip of the syringe for illustration purposes, in a real case it should be fully inside the tip of the syringe. It should not be allowed to fall into the barrel of the syringe.

Biologically Active Embolic Agents

MODIFIED COILS

Experiments have been performed in animal models with platinum coils whose surface has been modified with biologically active substances such as extracellular cellular matrix proteins, polymers, cytokines, or growth factors to modify thrombogenicity and inflammatory cellular response. Radioactive coils have also been used. Coils embedded with fibroblasts have been used in endovascular cerebral aneurysm repair in animal models with promising results. These modified coils are being developed to enhance tissue organization and fibrosis in aneurysms so that compaction of coils and recanalization

and growth of the aneurysm are prevented. In animal models, these biologically active coils have had encouraging (statistically significant) results.⁵⁻⁸ These new devices await human trials and validation.

GENE THERAPY

Gene therapy is a technique that allows a gene with a desired function to be inserted into a defective cell to correct a genetic error or to introduce a new function to the cell. However, lifelong replacement is needed to have continued benefit from the gene therapy. Vectors in the form of viruses may provide this prolonged gene expression in a large cell population of the target tissue or organ. Although gene therapy has been researched

extensively for years, many technical and conceptual obstacles remain before it can become a routine therapy.⁹

In the future, endovascular techniques may play an important role in the delivery of gene therapy. Vascular gene therapy may be performed *in vivo* (direct gene transfer) and *ex vivo* (cell-based transfer). The *in vivo* transfer of genetic material into a vessel wall does not require cell harvest or culture. The vector delivery may be performed with double balloon catheters or hydrogel-coated balloons. This technique has been used successfully in animal models to inhibit neointima formation after angioplasty or promote collateral vessels in an ischemic heart. Although a relatively simple technique, its limitation is low gene transfer efficiency.⁹ Adenovirus vectors have been attached to coils prior to their use for embolization of a cerebral aneurysm to modulate function of endothelial cells that eventually migrate to the neck and isolate the aneurysm with a layer of neointima.⁹⁻¹²

Another technique involves culturing target cells *in vitro*, transducing the desired gene into these cells, and reintroducing the cells in the desired location. Coils or stents embedded with modified cells may be used as the delivery system. The next generation of delivery systems may be constructed from biodegradable substances.⁹

PARTICULATE EMBOLIC AGENTS

Bland Embolics

GELATIN SPONGE

Gelfoam (Pharmacia and Upjohn, Kalamazoo, MI) and Surgifoam (Ethicon Inc, Somerville NJ) (Fig. 1) are inexpensive gelatin sponges. They are available in sterile sheets or as powder (Gelfoam). When used for vascular embolization (off-label use but within the standard of care), the gelatin occludes the vessels and induces vascular thrombosis and vessel wall inflammation. Within a few days to weeks, the gelatin disintegrates and allows vascular recanalization.^{3,13} Because of this property, gelatin foam is useful in treatment of bleeding related to peptic ulcer disease or trauma, in which healing of the underlying lesion is expected. It is also potentially useful in temporary devascularization of tumors that are bleeding or solid organs prior to resection to minimize blood loss.³

When small branches need to be embolized, such as left gastric artery branches or pancreaticoduodenal branches of the gastroduodenal artery supplying a bleeding peptic ulcer, gelatin sponge slurry may be used. To form the slurry, the foam is cut into 1- to 2-mm pieces and loaded into a 10-mL syringe after the plunger is removed. After the plunger is replaced, it is connected to another 10-mL syringe filled with dilute (1:1) contrast

material via a three-way stopcock. (Fig. 1) The contrast material and gelatin foam are pumped back and forth to create a slurry. More mechanical fragmentation of the gelatin foam may be achieved by leaving the stopcock only partially open, leading to a more uniform slurry mixture. This slurry is then slowly injected (through a conventional catheter or microcatheter) into the target vessel under fluoroscopic guidance until near stasis is achieved in the distal branches. Care should be taken not to cause reflux of gelatin foam out of the target artery. The Gelfoam pieces in the slurry mixture have a tendency to float in a nondependent position. To avoid accumulation of the macerated pieces at the back of the syringe, the syringe tip should be pointed up during the injection.³

Gelfoam (Pharmacia and Upjohn) powder particles range in size from 40 to 60 μm ; however, because of clumping, it causes occlusion of vessels 100–200 μm in diameter. This level of embolization leads to more severe ischemia than slurry or torpedoes. Gelfoam powder may be used for preoperative embolization of solid organs or tumors in solid organs. It should not be used to embolize hollow viscera because of the risk of necrosis.³

COLLAGEN PREPARATIONS

Many collagen preparations (in powder, sponge, and mesh forms) are available for topical use to achieve hemostasis during surgery. An example is Avitene (Davol, Cranston, RI), a substance derived from a bovine source. Avitene collagen fibers are 5 $\mu\text{m} \times 70\text{--}200 \mu\text{m}$ and, because of aggregation, cause vascular occlusion at the 25- to 250- μm level. The microfibrils are easily suspended in contrast material and delivered through microcatheters.³ Avitene causes more granulomatous reaction than the gelatin foam products.¹⁴⁻¹⁶ When microfibrillar collagen is used as an embolic agent (in an animal trial), only partial recanalization of vessels occurs in 2 weeks, compared with total recanalization of vessels embolized with gelatin foam. At 2 months, however, the vessels are completely recanalized as the collagen is resorbed.¹⁷ Collagen products are useful for preoperative or palliative tumor or organ embolization. Use as part of a chemoembolization mixture for treatment of liver metastasis from colon cancer has also been described.¹⁸ However, the use of collagen products has declined in favor of polyvinyl alcohol preparations and new spherical embolics.

DEGRADABLE STARCH MICROSPHERES

Spherex[®] (Pharmacia, Erlangen, Germany) microspheres are biodegradable starch microspheres. They are deformable to allow easy passage through microcatheters. The starch is rapidly metabolized (half-life of 25 minutes), causing only short-lived but intense ischemia. Its primary application is for chemoembolization. When either coadministered with chemotherapy or

administered before and after intra-arterial infusion of chemotherapeutic, it increases flow to low-flow areas in hypovascular tumor after the normal tissues with relatively high flow are temporarily embolized at the precapillary level. The embolization after the infusion leads to increased dwell time and exposure to chemotherapy and drug concentration in the tumor.¹⁹⁻²¹ It has been shown that when cisplatin is administered with degradable starch microspheres, the tumor tissue concentration is four times that after intra-arterial infusion of cisplatin alone.^{19,21} Similar results have been obtained with other drugs as well.²²

POLYVINYL ALCOHOL PARTICLES

Polyvinyl alcohol (PVA) is a substance that is available in blocks, sheets, or powder form with size ranging from 45 to 1180 μm (Fig. 2). When used as an arterial embolic, it leads to permanent occlusion of the vasculature and subsequent formation of thrombus.²³ In its amorphous particulate form, it has a tendency to clump into aggregates, resulting in occlusion at a level of vessels larger than the size of the particles. If the suspension of particles is too concentrated, it can lead to occasional occlusion of the catheter lumen. Besides using a less concentrated suspension, using appropriately sized particles for the catheter helps to avoid clogging the catheter. The PVA particles may be suspended for injection by pouring a 1-mL vial of particles into 50 mL of dilute contrast material in a sterile metal bowl. Agitation by placing the tip of a 3- to 5-mL syringe below the surface and stirring the mixture suspends the particles. Care is taken not to cause air bubbles, as bubbles trap the particles, leading to larger aggregates. Using contrast dilution recommended by the manufacturer for each size of particles helps lessen the effect of buoyancy and improve suspension of the particles. An alternative is to use a method similar to that

described earlier for making gelatin foam slurry. A less concentrated suspension should be used for smaller or less vascular territories. Like gelatin foam, PVA particles tend to float in contrast material, and to avoid clumping at the back of the barrel, the syringe tip must be pointed upward during injection.³ PVA use has been described in treatment of hypervascular tumors, chemoembolization of tumors, and organ ablation. Distal embolization with particles has also been described in treatment of lower gastrointestinal bleeding; however, caution is advised as overembolization and proximal embolization lead to bowel necrosis.²⁴

SPHERICAL EMBOLICS

In the past few years, a variety of spherical embolic agents have come to market and become increasingly popular. Compared with amorphous PVA particles, the spherical embolics should be increased in size by 100 to 200 μm to achieve the same level of occlusion. The increase in size is required because these new spherical embolics are compressible. Although they may be easier to use, none of the bland variety has been proven to be more efficacious than the others. Each of the spherical embolics is compressible and hydrophilic, facilitating flow through the delivery catheter and microvasculature. Contour SE Microspheres (Boston Scientific, Natick, MA) are spherical (nonhydrogel) PVA particles.²⁵ Bead Block (Biocompatibles UK Ltd, Farnham, Surrey, UK) microspheres are manufactured from PVA hydrogel. For easy visualization in the delivery syringe, Bead Block microspheres are tinted blue.²⁶ Embospheres (BioSphere Medical, Inc., Rockland, MA) are calibrated, spherical, hydrophilic microporous spheres composed of triacryl-gelatin. Embospheres are approved for embolization of hypervascularized tumors, arteriovenous malformations (AVMs), and uterine fibroids.²⁷⁻²⁹

Figure 2 (Left) Spherical polyvinyl alcohol (PVA; Contour SE) preparation. It comes suspended in saline for prehydration. (Right) The vial and the particles on the towel surface are amorphous PVA particles. They are supplied in a powder form, which needs to be suspended in dilute contrast material as described in the text.

Pharmembolic Particles

BIOLOGICALLY ACTIVE PARTICLES

Microspheres made from a variety of materials are under development and testing. Besides the spherical shape, compressibility, and hydrophilic nature described earlier, particles incorporating radioactive or chemotherapeutic agents are available or on the horizon. Biocompatibles UK Ltd has developed hydrogel PVA-based microspheres that allow elution of doxorubicin at a controlled rate. Trials are under way to determine their efficacy in humans. If successful, they may become the chemoembolization technique of the future. A similar technology may be used for other drugs and indications.^{3,26} SIRTEx is developing Dox-Spheres[®] (SIRTEx Medical Limited, Lake Forest, IL) in which doxorubicin is incorporated into spheres made from a biodegradable matrix, allowing controlled release of the active drug from the matrix.

CELLS FOR TRANSPLANTATION

For potential cure of type 1 diabetes, islet cells (encapsulated or nonencapsulated) may be infused through a percutaneous portal vein access to perform islet cell transplantation. With new sirolimus-based (steroid-free) antirejection protocols and graft islet cells from two (rarely three) donors, more than 80% of patients have been able to discontinue insulin. This option is currently restricted to patients with severe glycemic lability. It has the potential to become the standard of care in the future.³⁰

LIQUID EMBOLICS AND TISSUE ABLATIVE AGENTS

Unlike particles, which are lodged at a precapillary level or earlier, liquid agents can pass through the capillary bed and into the venous circulation. This feature makes them desirable when tissue ablation is the goal. They are used for ablation of tumors, organs, veins, or vascular malformations. Vascular occlusion results from a combination of thrombosis and destruction of the vessel endothelium, usually permanent.³ Because of the radiolucent nature of many liquid sclerosants and their deeper penetration into the vascular tree, their distribution is more difficult to control, increasing the risk of nontarget embolization. As an example, when dehydrated alcohol is used to ablate a kidney tumor, alcohol shunted into the venous system is harmless because of rapid dilution in the high-flow renal venous system. However, if the alcohol is perfused through retroperitoneal branches communicating with perineural vasculature (which may not be seen arteriographically and does not allow rapid dilution), paralysis may occur. Whenever possible, use of an occlusion balloon to deliver liquid sclerosants is recommended. For kidney ablation

or kidney tumor ablation, a common technique is to inflate the occlusion balloon in the renal artery or its branch and inject contrast material to determine the volume of contrast material needed to fill the kidney or the tumor to capillary phase. The balloon is then deflated to allow the contrast material to wash out. The balloon is then reinflated and the alcohol is injected at the same rate as the previous contrast injection. The balloon is kept inflated for 3–5 minutes to achieve tissue ablation and vascular thrombosis. The balloon catheter lumen must be aspirated prior to and while deflating the balloon to remove any residual alcohol and debris in the artery. This helps to prevent reflux of the debris into the aorta. If an occlusion balloon cannot be used, the alcohol can be made partially radiopaque by mixing it into an emulsion with ethiodized oil (Ethiodol) in an 8:2 or 7:3 ratio.³¹ The fluoroscopic visualization of suspended oil droplets makes it possible to infer the flow of the alcohol. Ethiodol also helps improve the distribution and embolic effect of the alcohol.³²

The Trufill n-BCA Liquid Embolic System (Cordis, Miami Lakes, FL) comprises *n*-butyl cyanoacrylate (n-BCA) (two 1-g tubes), Ethiodol (10 mL), and tantalum powder (1 g) (Fig. 3). They may be mixed in a variety of combinations to be injected through a microcatheter to embolize. The mixture is liquid during delivery, and it hardens to form a solid material on contact with ions in the blood. Because of its low viscosity, n-BCA is easy to deliver through microcatheters. Mixture with Ethiodol or tantalum powder allows visualization of the normally radiolucent glue during embolization. Tungsten powder may be substituted for tantalum. Tantalum increases the time to the initiation of polymerization, and Ethiodol increases the polymerization time itself. Glue-to-Ethiodol ratios of 1:1 to 1:4 are most commonly used. The interventionalist needs to be familiar with the linear relationship between glue dilution and polymerization (1 second at 1:1 and 4 seconds at 1:4 dilution).³³ Only D5W flushes should be used, as the monomer polymerizes when it comes into contact with ions. Polycarbonate may be destroyed by n-BCA. Therefore, polypropylene syringes should be used. To achieve effective embolization and to prevent complications while using n-BCA, training on bench-top flow models is recommended. The training allows the interventionalist to achieve the comfort level needed for its use. Complete description of the technique and the finer points is beyond the scope of this review. The Trufill embolic is approved for use in devascularization of cerebral AVMs prior to surgical resection.³⁴ Many off-label uses have also been described, including thoracic duct embolization, peripheral AVM embolization, and endoleak embolization after aortic endograft placement.

n-BCA causes an acute inflammatory reaction in the vessel wall and perivascular tissue, eventually

Figure 3 The TruFill system comes with Ethiodol (shown), n-BCA, and tantalum powder (not shown). Different ratios of these materials may be used for embolization. Ethiodol may also be used with dehydrated alcohol and as part of a chemoembolization mixture.

progressing to a granulomatous reaction and fibrosis. If a solid glue cast of the lesion is not formed, recanalization may occur. Extravascular extrusion of the glue has also been observed.³³

Liquid sclerosants (sodium tetradecyl sulfate or boiling contrast material) may also be used in the venous system. When they are used to ablate the gonadal vein in the treatment of a varicocele, the inguinal ring must be compressed to prevent reflux into the scrotum and testicular infarction.³⁵ In the United States, liquid sclerosants for gonadal vein ablation are rarely used now and have largely been replaced by coils. In today's practice (in the United States), the use of sodium tetradecyl sulfate (Sotradecol), boiling contrast material, and hypertonic glucose is rare or nonexistent.³

NONEMBOLIC PARTICULATES OR TISSUE ABLATIVE AGENTS

SIR-Spheres[®] (SIRTeX Medical) are radioactive 35- μ m microspheres (made of resin or ceramic) containing radioactive yttrium 90. On the average, β radiation emitted by the spheres penetrates 2.4 mm into the tissue. Yttrium 90 has a half-life of $\sim$ 64 hours and therefore minimal activity (2.5% of the original activity) remains after 2 weeks. The spheres are selectively infused in the blood vessel feeding the area of interest, trapping the SIR-Spheres[®] at a precapillary level. The primary mode of action for these spheres is radiation (selective internal radiation therapy), not occlusion of the tumor

vascular bed. It has been shown that in treatment of unresectable metastatic liver tumors from colorectal cancer, if a single dose of SIR-Spheres is administered with regional hepatic arterial chemotherapy with floxuridine, it is more effective in increasing tumor response and progression-free survival than the same hepatic arterial chemotherapy alone. Similarly, in treatment of liver-dominant metastatic colon cancer, if used in conjunction with intravenous fluorouracil/leucovorin therapy, response and time to progression increase.³⁶⁻³⁸

TheraSphere[®] (MDS Nordion, Toronto, Canada) also uses yttrium 90 as its therapeutic agent. However, the delivery vehicle is 20- to 30- μ m glass microspheres.³⁹

Hyperthermia is a technique for destroying cancer cells by raising the temperature of the tumor. Radiofrequency current and focused ultrasound are two examples of the percutaneous methods to achieve tumor hyperthermia. SIRTeX Medical is developing and testing Thermo-Spheres[®], small magnetic microspheres that can be delivered into the tumor by transcatheter methods and used to produce localized heating from within the tumor itself, destroying the tumor. Thermo-Spheres[®] are magnetic iron oxide nanoparticles encapsulated with a polyester coating to form 32- μ m particles.^{36,40}

MTC-Dox (FeRx Inc) uses a magnetic targeted carrier (MTC) drug delivery system. Carriers are 1- to 3- μ m particles of metallic iron and activated carbon. The activated carbon component of the particle is used to

absorb passively doxorubicin prior to the delivery. The drug is then slowly released after an external magnet apparatus is used to extract the particles out of the microvasculature into the tumor during the first pass. Once trapped, doxorubicin destroys the tumor locally. Although the parent company FeRx Inc is now defunct, the technology or its iterations may still prove promising in the future.⁴¹

CONCLUSION

Interventionalist radiologists have many therapeutic agents at their disposal. The intra-arterial therapies are in their infancy and the future holds much promise. The potential applications for catheter-based therapy will increase as the more products under development come to market and the spectrum of available products widens. It is incumbent upon interventional radiologists to be familiar with the biological properties, mechanism of action, and applications of these novel agents to stay at the "bleeding edge" of catheter-directed therapy.

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