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LABORATORY INVESTIGATION

A Preclinical Study of the Safety and Efficacy of Occlusin™ 500 Artificial Embolization Device in Sheep

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Abstract
Introduction This study evaluated the safety, effectiveness, and biodegradation of a new embolic agent, Occlusin™ 503 Artificial Embolization Device (OCL 503). The agent consists of biodegradable poly-lactic-co-glycolic acid microspheres (150–212 μm) coated with type I bovine collagen and was compared with Embosphere® Microspheres (300–500 μm) in this controlled study of uterine artery embolization (UAE) in sheep.
Methods Unilateral UAE was performed in 32 adult ewes randomly assigned. Vessels were embolized to effective stasis. The cohort was divided into four groups, which were sacrificed at 1, 3, 6, and 12 months.
Results Both agents were 100% effective in achieving stasis. At 6 months, all OCL 503-treated arteries were occluded, the microspheres degraded with time, and at 12 months all four animals examined demonstrated recanalization. OCL 503 was found in the untreated uterine artery in one animal with no other evidence of non target embolization. In the Embosphere-treated group, all vessels remained occluded and microspheres were detected in the contralateral uterine artery in 6 of 15 examined vessels and in 10 vaginal, 2 ovarian, and 1 vesical artery. No procedural-related complications were seen in either group.
Conclusions OCL 503 is as effective an embolic agent as Embosphere® Microspheres when embolizing ovine uterine arteries and resorbs with time, allowing recanalization of the treated arteries. No device-related issues or adverse events were observed.

Keywords Uterine artery embolization · Embolic agent · Recanalization · Biodegradable · PLGA

This work was conducted at the University of Alberta, Edmonton, Ab, Canada.

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Introduction

Occlusin™ 500 Artificial Embolization Device (OCL 500, *IM*Biotechnologies Ltd., Edmonton, AB) is a novel biodegradable embolotherapeutic agent consisting of poly(lactic-*co*-glycolic acid) (PLGA) microspheres coated with type I bovine fibrillar collagen. Manufactured in multiple size ranges, OCL 500 is intended as an artificial embolization

device in the treatment of solid hypervascular tumors, including uterine fibroids. Similar to commercially available embolotherapeutic agents, OCL 500 physically occludes blood flow in vascular structures and, in addition, binds platelets, effectively consolidating clot formation and inducing further ischaemia.

OCL 503, one member of the OCL 500 product line, was designed for delivery through microcatheters. This study evaluated the safety, efficacy, and biocompatibility of OCL 503 in sheep in comparison to EmboSphere® Microspheres (Biosphere Medical Inc, Rockland, MA), a commercially available artificial embolization device. This study also examined other important device-related issues, including ease of administration, stability of suspended microspheres, extent of target vessel occlusion, rate of resorption, migration to nontarget tissues, recanalization of the target vessel, and local tissue reaction.

Materials and Methods

This study was conducted at the Pediatric Cardiovascular Research Laboratory and the Metabolic Unit at the University of Alberta, Edmonton, Alberta. The University of Alberta is accredited by the Canadian Council on Animal Care and the National Institutes of Health. Animals were housed under conditions consistent with all provincial and national regulations and received standard medical care from animal health technicians.

Thirty-two one-year-old female Suffolk cross sheep were identified with unique ear tags. All animals were weighed and paired by weight. One animal of each pair was randomly assigned to receive one of the embolic agents in this study; the other animal was automatically scheduled to receive the other agent. Each pair of animals was randomly assigned to one of four time groups (1 month, 3 months, 6 months, or 12 months) before embolization.

Veramix® sponges (Pharmacia and Upjohn; Orangeville, ON) impregnated with medroxyprogesterone acetate were inserted into the vagina of each animal 13–15 days before the procedure [1, 2]. On the day before the procedure, the vaginal sponge was removed, a cannula inserted into the jugular vein, and 400 international units of pregnant mare serum gonadotropin (Folligon® Injection; Intervet Canada Ltd, Whitby, ON) injected intramuscularly (IM). Animals also received IM injections of Metacam® (0.2 mg/kg; Boehringer Ingelheim Vetmedica; Burlington, ON) on the day of the procedure, the day after the procedure, and then as required for pain relief. Each animal received either 1 g of ampicillin (Novopharm, Toronto, ON) by intravenous drip during the procedure followed by 500 mg BD given IM for 2 days after the procedure or 2 mg/kg of Ceftiofur hydrochloride (Pharmacia and Upjohn) IM on the day of the procedure and on the following day.

Animals were kept in a flock in an outside pasture. One week before the procedure, animals were brought indoors, sheared, and housed in individual pens within sight of other sheep. After the procedure, the animals were kept inside until their coat was long enough or the outside temperature warm enough for them to be released back into the outside flock.

Anesthesia was induced with isoflurane or enflurane and maintained with the addition of 5 ± 2% nitrous oxide. All animals were intubated and ventilated until recovery of spontaneous respiration. Both femoral artery sites were prepped and draped with strict adherence to sterile technique. One of the femoral arteries was randomly chosen and punctured using standard percutaneous Seldinger technique. If the first puncture was unsuccessful, the contralateral femoral artery was accessed. A 5-French vascular sheath was then placed in the artery and a 5-French C2 or Rim diagnostic catheter (Beacon Tip Torcon Advantage Catheter, Cook Incorporated, Bloomington, IN) used to catheterize the internal iliac artery and image the uterine artery (UA). The UA was then selectively cannulated by using a 2.3-French Rapid Transit or 2.3-French Prowler Select Microcatheter (Cordis Corporation, Markham, ON) using road mapping under fluoroscopic guidance (Siemens Sire Mobile 2000 C-arm, Siemens Canada Ltd. Burlington, ON). The UA contralateral to the femoral puncture site was preferentially catheterized. The ipsilateral artery was chosen if the contralateral vessel could not be clearly identified or catheterization attempts were unsuccessful.

Once the position of the microcatheter was confirmed within the UA, either OCL 503 (150–212 μm, 400 mg/vial; *IM*Biotechnologies Ltd.) or Embosphere® Microspheres (300–500 μm, 2-ml syringes; BioSphere Medical) suspended to neutral buoyancy using Omnipaque™ 300 or Omnipaque™ 240 (Amersham Health, Oakville, ON) and normal saline was injected into the target artery. The embolic agent was administered in small (<1 ml) aliquots until effective stasis had been achieved. Effective stasis was deemed reached when injected contrast remained in the main UA for five or more cardiac pulsations, indicating near static flow. After the procedure, the microcatheter, diagnostic catheter, and vascular sheath were removed. Hemostasis at the puncture site was achieved by using manual pressure. Following closure, the anesthetic agent was discontinued and the animals ventilated until the return of normal respiration.

Full procedural data was recorded for all animals. Fluoroscopic time was recorded for 50% (8/16) of the animals in each group. All procedures were performed by a single interventional radiologist (RJO).

Animal weights and blood samples were collected as scheduled on days −1, +1, +7, and +14 and 1, 2, 3, 6, and 12 months after the procedure. Additional weights and blood samples were collected as requested by the study veterinarian. Hematological and clinical chemistry analyses of the blood samples were conducted at Central Laboratory for Veterinarians, Ltd. (Edmonton, AB).

Groups of eight animals (4 treated with OCL 500 and 4 treated with Embosphere Microspheres) were sacrificed at 1, 3, 6, and 12 months according to the study protocol. Animals were euthanized with 120 mg/kg of sodium pentobarbital (Euthanyl®, Bimeda-MTC Animal Health Inc., Cambridge, ON). A standard postmortem examination was performed with specific examination of the target and nontarget uterine arteries. Tissues were collected into formalin for histological examination. Tissue samples were processed, embedded in paraffin, and histological sections were prepared by Histobest Inc. (Edmonton, AB) using standard procedures. All carcasses were incinerated after postmortem examination and tissue collection.

The safety and biological data recorded in this preclinical study was analyzed according to the study protocol. Safety analyses consisted of the clinical and laboratory effects observed in treated animals. The statistical analysis was primarily descriptive. Statistical significance for the fluoroscopic time, amount of embolic material required to reach effective stasis, and mean weight gain in both groups of treated animals was determined using the one-tailed Student's *t* test.

Results

Embolization

The uterine arteries were clearly identified in all 32 animals and embolization to effective stasis was achieved in all cases (Left UA—25 sheep, right UA—7 sheep). Postprocedure course was uneventful for all but one animal, and there were no angiographic or anesthetic-related complications.

The fluoroscopic time required to achieve effective stasis was not significantly different between OCL 503 (8.9 ± 2.7 minutes) and Embosphere® Microspheres (8.1 ± 3.6 minutes) study groups ($P = 0.32$; Table 1). The mean number and SD of vials of OCL 503 (0.8 ± 0.3) or syringes of Embosphere® Microspheres (0.9 ± 0.3) used to reach effective stasis in the two treatment groups was not significantly different ($P = 0.31$; Table 2).

Animal Health

Animal G186 developed an infection at the site of the preprocedure jugular cannulation the day after embolization with OCL 503 and received hot compresses, Excenel for 6 days, and Oxytetra-cycline LA for 2 days. The infection appeared to clinically resolve within 8 days. However, 3 weeks after treatment, G186 began to exhibit difficulty walking. Clinical symptoms and disability became more pronounced with time and the animal was humanely sacrificed 7 weeks after the procedure, 5 weeks before its scheduled sacrifice. Postmortem examination demonstrated an abscess in relation to the fifth cervical vertebral body. This appeared to have arisen by extension from the infection at the site of the jugular cannulation and was deemed unrelated to the embolization procedure. All other animals remained in good clinical health during the study and were sacrificed as scheduled.

Table 1 Fluoroscopic time to achieve effective stasis in each group of sheep

Treatment group	No. of sheep	Minutes (Mean ± 1 SD)
OCL 503	$n = 8$	8.9 ± 2.7
Embosphere® microspheres	$n = 8$	8.1 ± 3.6

Not significantly different: $P = 0.32$, single-tailed Student's *t* test

Note that the fluoroscopic time was only recorded in 50% of the treated sheep (8/16 in each treatment group)

Table 2 Embolic agent (vials/syringes) required to achieve effective stasis in the uterine artery

Treatment group	No. of sheep	Units (Mean ± 1 SD)*	Units (range)
OCL 503 (400 mg vials)	$n = 16$	0.8 ± 0.3	0.4–1.3
Embosphere® Microspheres (2 ml syringes)	$n = 16$	0.9 ± 0.3	0.3–1.6
Single-tailed Student's *t* test	–	$P = 0.31$	–

* Not significantly different: $P = 0.31$, single-tailed Student's *t* test

Animal Weights

The mean weight of sheep in each treatment group is shown in Fig. 1. Both of the groups gained weight with time as expected, and there was no significant difference between the two groups.

The sheep embolized with Embosphere® Microspheres appeared to gain weight more slowly between 6 and 12 months than sheep treated with OCL 503. This was due primarily to the weight loss of 3 kg in sheep B29, whereas all other sheep gained between 12 and 26 kg during this period. B29 was in good health at the time of sacrifice, and no physiological reason was identified for its failure to thrive. Sheep G186 lost 10 kg in weight during the past 3 weeks of its life as a consequence of its spinal abscess.

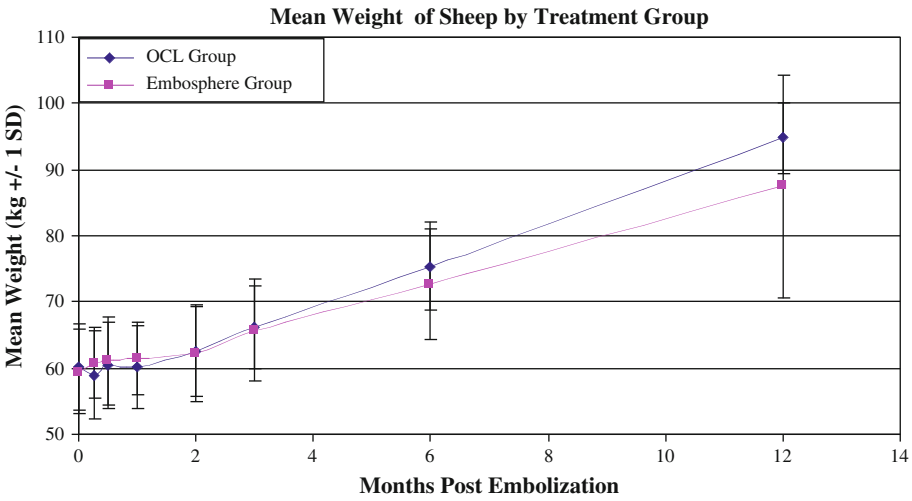

Fig. 1 Mean weight of sheep by treatment group. The mean weights are not significantly different from each other: $P > 0.19$–0.46 single-tailed Student's t test. The error bars represent one standard deviation (SD)

Clinical Laboratory Data

Blood samples were collected the day before the procedure (day −1) and at 1, 7, and 14 days and 1, 3, 6, and 12 months afterwards. Standard clinical laboratory tests for haematology and clinical chemistry parameters were performed. An internal reference range, the range of clinical laboratory data on day −1 for the 32 sheep used in this study was used to assess individual and group mean values.

There were no differences at any time point between the OCL 503 group and the Embosphere® Microsphere group in any of the hematological or clinical chemistry parameters examined. There were minor fluctuations in the differential white cell counts, serum electrolytes, creatinine phosphokinase (CPK), and liver enzymes on the day after the procedure. These transient abnormalities generally resolved by 1 week and were considered part of the normal physiological response to anesthesia and the embolization procedure.

Animal G186, which developed an abscess in a cervical vertebral body after internal jugular cannulation, had elevated muscle enzymes and phosphorus accompanied by clinical signs of stiffness prior to its termination. The changes in clinical chemistry parameters were clinically judged to be secondary to the effects of the abscess upon the musculoskeletal system.

Animal B183 had elevated CPK at 6 and 7 months after embolization with OCL 503 that returned to normal by 8 months. There were no abnormal clinical findings and the cause was never determined. This animal was normal at the termination of the study by gross and microscopic postmortem examination. In neither of these animals was the alteration in hematologic and clinical chemistry parameters thought to relate to the embolization procedure.

Postmortem Findings

The uterus and ovaries were exposed and examined in situ immediately postmortem. All treated arteries stood out as thickened, solid, rope-like cords 1 month post embolization. Arteries treated with OCL 503 remained firm and distended and could be clearly distinguished from the contralateral untreated arteries in animals sacrificed at 3 and 6 months postembolization, although the differences between treated and contralateral untreated arteries were less marked at 6 months. By 12 months, the uterine arteries treated with OCL 503 were visually and tactilely indistinguishable from the untreated contralateral arteries (Fig. 2A). The embolized arteries in animals treated with Embosphere® Microspheres remained unchanged in appearance and felt as thickened rope-like cords at all time points during the study (Fig. 2B). Infarction of uterine tissue was not observed at any time point in either treatment group.

Animal G186 was in good general body condition at gross postmortem despite her recent weight loss; the only abnormality was destruction of the vertebral body in an approximately 1-cm diameter spherical region consistent with an abscess. The abscess extended into the epidural space adjacent to and causing pressure on the spinal cord, but there was no extension of inflammation distal to the affected level. All other animals were in excellent body condition. Other than the thickening of occluded uterine and occasionally vaginal arteries, there were no gross postmortem abnormalities.

Histological Findings

Photomicrographs of the OCL 503 microspheres and Embosphere® Microspheres are shown in Fig. 3. Photomicrographs of cross-sections of the treated uterine arteries at 1, 2, 6, and 12 months post treatment with OCL 503 or

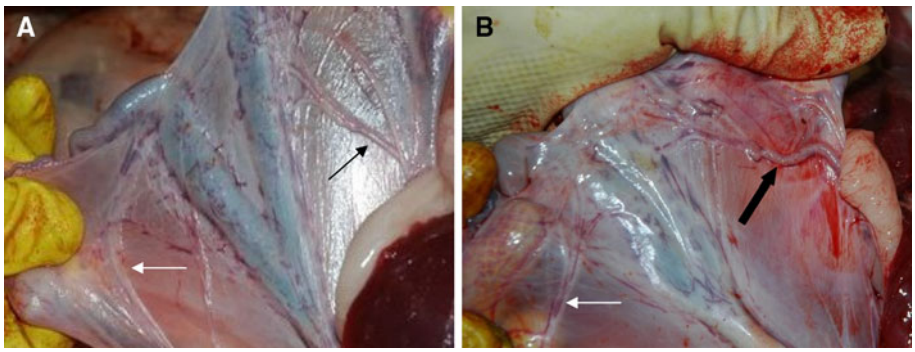

Fig. 2 Uterine arteries 1 year after embolization. **A** OCL 503 in the left uterine artery of sheep B43. **B** Embosphere® Microspheres in the left uterine artery of sheep B29. The OCL 503-treated left uterine artery (*black arrow*, **A**) was visually and tactilely indistinguishable from the right, untreated artery (*white arrow*, **A**). Both arteries were small and smooth to the touch. The left uterine artery of Embosphere Microspheres-treated sheep B29 (*thick black arrow*, **B**) remains highly distended and hard to the touch due to retained embolic particles. The untreated right artery is shown by a *thin white arrow* (**B**)

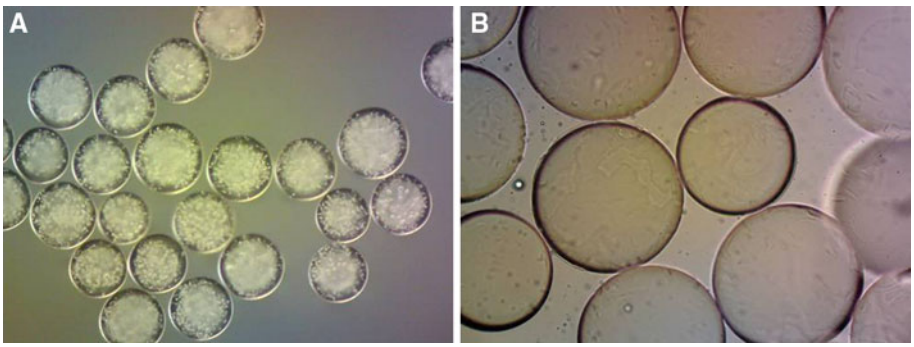

Fig. 3 Appearance of OCL 503 and Embosphere® Microspheres. **A** OCL 503 microspheres (×10) **B** Embosphere® Microspheres (×10). This phase contrast photomicrograph is representative of the microspheres used in this study

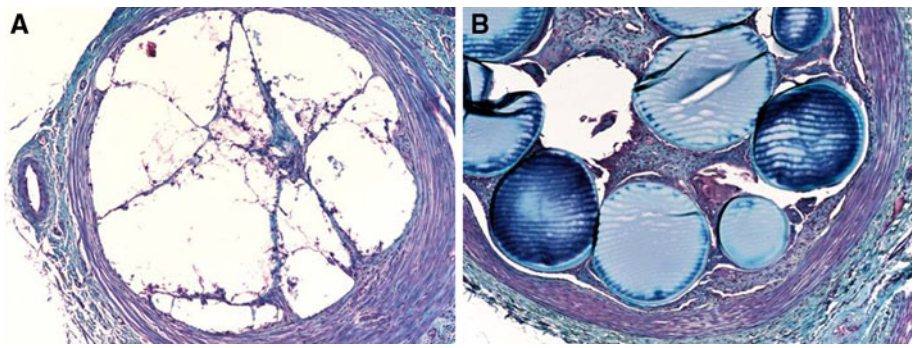

Fig. 4 Histological sections of sheep uterine arteries 1 month after UAE. **A** OCL 503 Microspheres (×100). **B** Embosphere® Microspheres (×100) 1 month after UAE the arteries treated with OCL 503 or Embosphere® Microspheres were fully occluded. The initially spherical OCL 503 microspheres showed profound shape changes and are beginning to biodegrade. The OCL 503 microspheres did not take stain (Masson's Trichome) and appear as white, irregular, shapes. The Embosphere® Microspheres retained their spherical shapes and stain blue. The folding and rippling appearance of the surface of the Embosphere® Microspheres are artifacts caused by tissue preparation and sectioning

Embosphere® Microspheres are presented in Figs. 4, 5, 6, 7. As shown in Fig. 4A, the initially spherical OCL 503 microspheres had profound shape changes 1 month after the procedure; as they began to biodegrade and conform to the interior of the vessel, fibrous connective tissue was seen as a matrix around and between the spheres (Fig. 4A). Three months after the procedure, the residual OCL 503 material is highly deformed and compressed into the center of the treated artery (Fig. 5A) as it continues to biodegrade and fibrous connective tissue completely occludes the treated arteries. Figure 6A shows that fibrous connective tissue appears to have replaced the inner luminal wall of the artery, which remained completely occluded 6 months after the procedure, although the OCL 503 microspheres

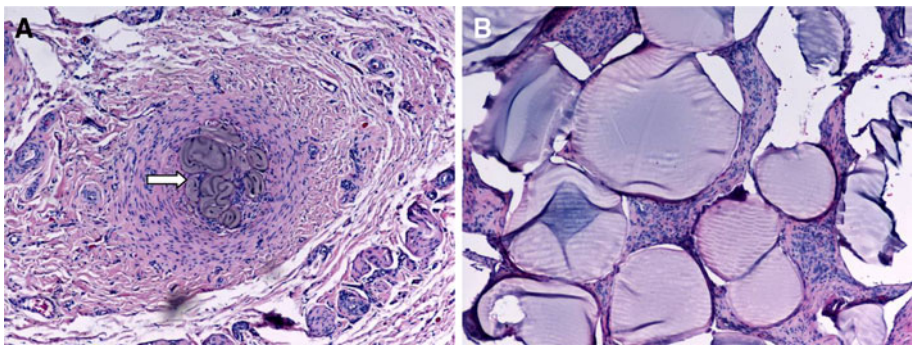

Fig. 5 Histological sections of sheep uterine arteries 3 months after UAE. **A** OCL 503 microspheres (×100). **B** Embosphere® Microspheres (×100) 3 months after UAE the uterine arteries treated with OCL 503 or Embosphere® Microspheres remained fully occluded. There were no identifiable intact OCL 503 microspheres, and the residual material was highly deformed and compressed in the center of the artery as it continued to degrade (*white arrow*). In other sections, even less OCL 503 microsphere material was visible. In contrast, the Embosphere® Microspheres retained their round shapes and the artery remained highly distended. The sections were stained with Masson's Trichome

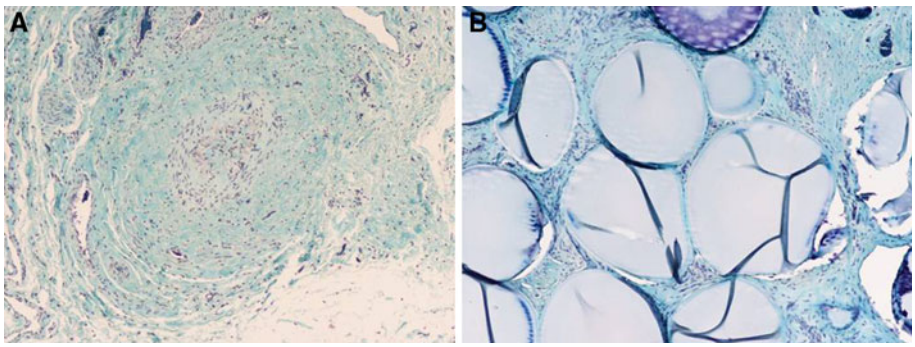

Fig. 6 Histological sections of sheep uterine arteries 6 months after UAE. **A** OCL 503 microspheres (×100). **B** Embosphere® Microspheres (×100) 6 months after implantation; uterine arteries treated with OCL 503 or Embosphere® Microspheres remained completely occluded. The inner luminal wall of shown artery treated with OCL 503 microspheres was replaced by fibrous connective tissue. No residual OCL 503 material was observed. The Embosphere® Microspheres retained their round shapes and the artery remained highly distended. Connective tissue was present between the Embosphere® Microspheres. Sections stained with Masson's Trichome

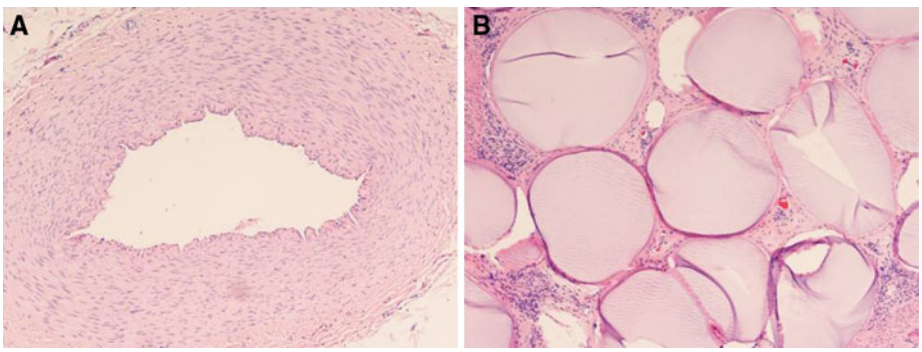

Fig. 7 Histological sections of sheep uterine arteries 12 months after UAE. **A** OCL 503 microspheres (×100). **B** Embosphere® Microspheres (×100) 12 months after UAE; the lumen of the uterine artery treated with OCL 503 microspheres had fully recanalized in three of four sheep and was partly recanalized in the fourth sheep. In contrast, the arteries treated with Embosphere® Microspheres remained fully occluded in all four of the treated sheep. Sections stained with Masson's Trichome

have completely degraded. Uterine arteries treated with OCL 503 had either fully recanalized ($n = 3$, Fig. 7A) or were in the process of being recanalized ($n = 1$) at 12 months. Recanalized vessels showed normal luminal architecture and were histologically indistinguishable from the untreated contralateral vessel.

The histological appearance of the Embosphere® Microspheres-treated arteries remained unchanged throughout the 12-month observation period (Figs. 4B, 5B, 6B, 7B) and the vessels remained completely occluded.

OCL 503 microspheres were found in the lumen of the treated artery (Fig. 4A) as well as its branches as far distal as the myometrium and occasionally into the endometrium. Embosphere® Microspheres had a similar qualitative distribution in the uterine vasculature. This distribution of OCL 503 embolic material in the treated vasculature is very similar to that described for trisacryl gelatine microspheres (700–900 μm) by Laurent et al. [3].

Microspheres of both types were embedded in a thin collagen matrix with small numbers of macrophages and occasional giant cells present in close proximity. However, inflammation was not a significant feature of the reaction to either type of microsphere.

Occluded arteries were identified by histological examination of tissues collected from 12 OCL 503-treated sheep and 16 Embosphere® Microsphere-treated sheep. Data for the 4 OCL 503-treated sheep sacrificed at 12 months were excluded from this analysis, because the treated arteries had either fully recanalized or were in the process of recanalizing. OCL 503 microspheres were found in 12 of 12 (100%) of the treated UA and of the untreated contralateral uterine vasculature in 1 of 12 animals (8%) but were not identified in the vaginal, ovarian, or vesical vasculatures in any animal. Embosphere® Microspheres were detected in 16 of 16 (100%) treated UA and in the contralateral uterine vasculature of 6 of the 15 examined vasculatures (40%). In addition, Embosphere® Microspheres were identified in the vaginal (10/16 animals; 63%), ovarian (2/16 animals; 13%), and vesical (1/16 animals; 6%) vasculatures.

Discussion

Transarterial embolization (TAE) is a widely practiced endovascular technique to achieve effective vessel occlusion in a variety of conditions. Particulate embolic agents are widely utilized in this regard and in particular for the treatment of benign and malignant tumors. Commercially available agents include polyvinyl alcohol particles, trisacryl gelatin microspheres, polyvinyl alcohol particles, and gelatin sponge. One of the more common applications, and one that is widely practiced, is uterine artery embolization (UAE) for the treatment of symptomatic uterine fibroids. Embosphere® Microspheres are widely used in this area and therefore were chosen as the comparative agent in this study.

Embosphere® Microspheres possess many desired properties of an embolic agent: they have an established safety profile, are effective and predictable in occluding the target vessel, are compatible with angiographic contrast agents and equipment, in particular microcatheters, and are easy to prepare and introduce. OCL 500 in addition to fulfilling these criteria possesses one additional desirable characteristic: it is bioabsorbable, which warrants further discussion. In the specific case of UAE, complete temporary occlusion leads to infarction of the leiomyomas [4]. Treatment with a biodegradable embolic agent, such as OCL 500, would facilitate recanalization of the uterine vessels in the long-term. This would be a very desirable feature if future pregnancy is considered. Laurent et al. [5] hypothesized that devascularization of the uterine tissue post-UAE could affect all steps of pregnancy: from conception to delivery. There are other instances where a temporary occluding agent would be desirable: for the treatment of gastrointestinal hemorrhage; solid organ injuries, such as splenic embolization; and in tumor embolization, where repeat procedures are required. In this regard gelatin sponge (Gelfoam) often is used, because it is considered a temporary agent based on early recanalization, with the occluded vessel recanalizing in 2–4 weeks [6, 7]. The evidence for this exact time frame is limited, and there are many factors that influence when and, indeed, if a vessel will recanalize and cases of permanent occlusion with Gelfoam have been well documented [8].

The OCL 503 microspheres were reliably and consistently suspended in a solution of normal saline and contrast medium, and the resulting suspensions were easily delivered to the target vasculature through standard 2.3-French microcatheters. The microspheres were easy to use, did not clog the syringe or catheter, and the resultant suspension was clearly visible with fluoroscopy. Figure 3 shows the appearance of the microspheres.

No statistically significant differences were observed in the fluoroscopic time required to achieve effective stasis for OCL 503 or Embosphere® Microspheres (8.9 ± 2.7 vs. 8.1 ± 3.6 min; $P = 0.32$; Table 2). No statistically significant differences were seen in the number of vials of OCL 503 and the number of syringes of Embosphere® Microspheres required to achieve effective stasis (0.8 ± 0.3 vials vs. 0.9 ± 0.3 syringes; $P = 0.31$; Table 2). No local or systemic toxicities were observed in either treatment group. Transient changes were observed in hematology and clinical chemistry parameters 1 day after the procedure were generally resolved by 7 days and were observed in both treatment groups, with no significant differences.

The OCL 503 microspheres underwent profound shape changes in vivo as they were compressed and began to biodegrade (Fig. 4A). At 3 months, the residual OCL 503 material was highly deformed and compressed in the center of the artery (Fig. 5A). There was no detectable OCL 503 material present at 6 months (Fig. 6A). Fibrous connective

tissue formed around and between the OCL 503 microspheres, forming a matrix that held the microspheres in place as they degraded (Figs. 4A [1 month postprocedure] and 5A [3 months]). The fibrous connective tissue maintained complete occlusion of the treated artery at 6 months despite the complete disappearance of the OCL 503 microspheres (Fig. 6A). Arteries were fully recanalized ($n = 3$; Fig. 7A) or were in the process of recanalizing ($n = 1$) 1 year after embolization. In contrast, all arteries treated with Embosphere® Microspheres were fully occluded for the duration of the study (Figs. 4B, 5B, 6B, 7B). The long-term clinical advantages of recanalization cannot be determined from this study. It may be appropriate to develop a more rapidly degrading device for use in procedures where repeat embolization is required within a matter of weeks or a few months.

OCL 503 microspheres have several properties that work together to form a tight, efficient clot in the target location. The microspheres are relatively dense compared with other embolic agents, and this greater density slows their forward flow in the blood stream and decreases the risk of retrograde flow. The microspheres are noncompressible and bind platelets in a matter of minutes, effectively increasing the size of the microsphere particles. Furthermore, cross-linking of microspheres via platelet-platelet interaction can increase the effective size of the embolic as well as stabilize the resultant platelet-rich clot. OCL 503 microspheres (150–212 μm) were compared in this study with the nominally larger Embosphere® Microspheres (300–500 μm) based on these theoretical considerations.

The majority of the OCL 503 microspheres were found in the lumen of the treated uterine artery. Smaller numbers were found in the myometrial arteries and arterioles and fewer yet in mucosal arterioles. Microspheres also were found in the untreated contralateral uterine vasculature in one animal (8%). Embosphere® Microspheres had a similar qualitative distribution in the treated uterine vasculature but also were detected in the contralateral uterine artery in 40% of treated animals and in the vaginal (63%), ovarian (13%), and vesical (6%) arteries. Embosphere® Microspheres, which are compressible and less dense than the OCL 500 microspheres, may travel further down collateral pathways or be more susceptible to the effects of retrograde flow from the treated artery to other downstream vasculatures during the embolization procedure.

It has been reported in the literature that women treated with UAE are at risk of suffering premature menopause. The incidence increases significantly with age (2–3% of women younger than age 45 years vs. 15% or greater of women older than 45 years [9–11]. It also been reported that up to 44% of women have anastomoses between the uterine and ovarian arteries [12], and it can be speculated that older women are more susceptible to the effects of nontarget embolization of the ovarian vasculature through these anastomoses. Marx et al. [13] have suggested that embolization of the anastomoses before UAE may protect women from premature menopause. The use of denser, noncompressible microspheres, such as OCL 500, also may reduce the risk of this, and other, nontarget embolization.

In conclusion, OCL 503 was found to be safe and effective as an embolotherapeutic agent as tested. The localized tissue distribution observed with this product, coupled with its in situ degradation and absorption, suggests that OCL 503 may have a greater safety profile than many approved and marketed embolic devices, which can migrate to nontarget tissue or have been reported to extravasate from the target vasculature [3, 14, 15]. Additional work is warranted with this device.

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Conflict of interest Robert Polakowski, Jennifer A Biliske, Paul B Tiege, and Irwin J Griffith are former employees of ViTexx Medical Corp., which provided an operating grant that supported the study. Irwin J Griffith is a current employee of IMBiotechnologies Ltd. There are no other conflicts.

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