

Tegress™ Urethral Implant Phase III Clinical Experience and Product Uniqueness

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Advances in materials technology, coupled with a heightened understanding of wound healing and tissue-materials interactions in the lower urinary tract, have led to the development of a variety of new urethral bulking agents that are expected to be available in the near future. Experience with such bulking agents continues to grow and study results are disseminated as more clinical trials are initiated and completed. The intention of this report is to review the characteristics and initial clinical results for one of these new agents: Tegress™ Urethral Implant (C. R. Bard, Inc., Murray Hill, NJ). This material, with unique phase-change properties upon exposure to body temperature fluids, offers ease of injection and requires less volume for clinical effect than bovine collagen. Additionally, Tegress Urethral Implant performance in clinical trials has suggested improved durability and correspondingly higher continence and improvement rates versus bovine collagen. As these materials evolve, an understanding of preferential implant techniques is being gained also. Delivery method and implant site may prove to substantially alter the biologic activity of these compounds. As outlined in this review, experience with Tegress Implant resulted in changes in delivery technique that translated into improved materials and tissue interaction.

[Rev Urol. 2005;7(suppl 1):S22-S26]

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Key words: Bulking agents • Stress urinary incontinence • Surgery

Urinary incontinence affects an estimated 200 million men and women worldwide; in the United States alone, from 10% to 35% of women suffer from this condition.^{1,2} Genuine stress urinary incontinence (SUI) is the most prevalent form of incontinence among women, affecting approximately 30 million US women over age 18.³ With the continued aging of the population, genuine SUI will be an increasingly significant health concern and a condition associated with substantial medical and hospital costs. According to national

statistics, approximately 180,000 surgical procedures are now performed for genuine SUI each year in the United States and more than \$19 billion (2000 US dollars) is spent on urinary incontinence, alone.⁴ The lack of a single, reproducible, permanent, low-risk procedure has led to the development of minimally invasive options that provide the hope of reasonable efficacy associated with low morbidity. Reimbursement pressures have resulted in the increasing use of those interventions requiring fewer and/or shorter hospitalizations or those that can be performed entirely in an ambulatory care setting without general or regional anesthesia and no attendant recuperative facilities.

substance must be “safe and provide anatomic integrity.”¹⁰ In addition, the substance composition should ensure lack of migration, lack of local inflammation and chronic tissue changes; facility of agent use (ease of preparation); and an optimized host environment (hormonal environment, integrity of urethral mural components and periurethral fascia). Currently, human (autologous or allograft), xenograft, and synthetic materials are all undergoing evaluation as periurethral bulking agents.

There are several optimal attributes for bulking materials. For example, there should be minimal fibrosis associated with host-tissue response to the injected agent, little extracapsular

composed of uniform spheroidal particles with sizes greater than 110 microns (approximate size required to avoid migration). Migration is clearly influenced by the ability of host macrophages to phagocytize particles. Smaller particle sizes can migrate to distant locations, as is now clinically confirmed and commonly recognized with Teflon® injection. However, direct embolization of material, caused by high-pressure injection, resulting in material displacement into vascular or lymphatic spaces may also play a role in material dislocation. The recently reported carbon particulate migration probably represents high-pressure introduction of particulate material into the vascular system.^{10,13} It is recommended that implant technique rely on larger (ideally uniform) particle sizes administered with low-pressure injection instrumentation.

Ideal bulking agent materials should be associated with lack of migration, lack of local inflammation, and chronic tissue changes. In addition, it should demonstrate facility of agent use and an optimized host environment.

Bulking Agents

The implantation of bulking agents, most commonly collagen, has been used for the management of genuine SUI for more than a decade.⁵⁻⁷ This therapy has, however, been negatively affected by materials-related concerns, including limited durability of the bulking agent and antigenicity associated with bovine collagen.⁸⁻⁹ The recent US Food and Drug Administration approval of carbon particulate technology has provided another option for bulking, but one that is somewhat limited by difficulty with injection (due to carrier extrusion, resulting in injection needle obstruction).¹⁰ Ongoing clinical trials are evaluating several different materials with the goal of finding a better agent.

The successful use of lower urinary tract bulking agents requires ideal materials composition and the ideal

inflammatory response, and minimal resorption of injected material. The bulking agent should be biocompatible, produce little or no immunogenic response in the host (hypoallergenic), and be stable on injection (no in vivo separation of subcomponents).¹¹ The material, upon injection, should minimally deform the host tissues and not disrupt tissue planes (rheologic character, influenced by viscosity and surface tension of the device). The ideal scenario for any successful soft tissue bulking agent would be a single injection with permanent volume retention of the agent without migration, with partial or total incorporation into host lower urinary tract tissues. The currently available agents do not fulfill all of these criteria, and therefore new materials continue to be investigated.

Materials migration after injection remains more than a theoretic concern.¹² Bulking agents should be

Tegress™ Implant: Composition, Development, Indications

Ethylene vinyl alcohol (EVOH) copolymer suspended in dimethyl sulfoxide (DMSO), or Tegress™ Urethral Implant solution (C. R. Bard, Inc., Murray Hill, NJ), is being evaluated as an embolic agent and a bulking agent. It is a sterile, non-pyrogenic device composed of 8% EVOH copolymer (48 mole % ethylene with no additives) and DMSO (99.9% purity). The material is packaged in 3 mL vials that are sealed with silicone stoppers and aluminum closures. This agent was originally developed as an intravascular embolization agent, called Onyx® (previously known as Embolix, MicroTherapeutics, Inc., Irvine, CA), for use in disrupting blood flow. Onyx is currently under evaluation for the treatment of brain arteriovenous malformations, cerebral aneurysms, and hypervascular tumors of the head and neck. The intravascular and intracranial applications of Onyx require

visualization under fluoroscopy during injection. Therefore, Onyx contains micronized tantalum powder, a contrast agent. Because radiographic visualization of a urethral bulking agent is not required (other than for research purposes) Tegress does not contain tantalum.

and polyvinyl alcohol (PVA), both of which have a long history as implant materials. Polyethylene is used in numerous implant applications, including orthopedic (surgical spinal cable, prostheses for spinal disk replacement, and in joint implants for the acetabular, patellar, and tibial surfaces)

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In addition to treatment in the cerebral vasculature, the Onyx formulation with tantalum is being evaluated under the product name Eteryx (Enteric Medical Technologies, Inc., Foster City, CA) for the treatment of gastroesophageal reflux disease (GERD). The use of Tegress as a urethral bulking agent in the urinary tract began recently, arising from the unique characteristics of the material. Upon injection of and exposure to the solution (blood or extracellular space) at physiologic temperatures, the DMSO diffuses from the hydrophobic copolymer and causes the EVOH to precipitate into a complex cohesive spongiform mass. This phase change requires diligent separation of agent and body temperature fluids prior to implantation. The phase transformation takes place rapidly, with the spongiform mass developing within 60 seconds post injection. Based on these unique findings and the demonstrated biocompatibility of the agent, the applicability of Tegress as a urethral bulking agent was analyzed in a large-scale new-device trial supervised by the US Food and Drug Administration (FDA).

During the development of Tegress, options for constituents in the actual formulation of the product included several substances. EVOH is derived from the homopolymers polyethylene

and otorhinolaryngologic (auricular reconstruction) indications. In addition, polyethylene is a United States Pharmacopeia (USP) reference standard often relied upon as a negative polymer control during biocompatibility testing. Additionally, PVA is used clinically in topical ophthalmic solutions, plasma expanders, and as a permanent particle embolization material. EVOH copolymer is used as a hemodialysis and plasmapheresis membrane.

The carrier solvent DMSO has been used in a variety of medical applications. It is commercially available in the United States (RIMSO-50, Edwards Lifesciences Research

Tegress has been found to be non-carcinogenic in a *ras-H₂* transgenic mouse model for carcinogenicity. Additionally, chronic (2-year) urethral implantation studies in mini-swine demonstrated that Tegress becomes permanently encapsulated with tissue in-growth into the porous material structure, with no evidence of distant material migration to other sites, as determined by macro- and microscopic examination of tissue specimens. Over the same time frame, a comparison of the area (volume) of injected material revealed the volume to be approximately unchanged between initial and later observation intervals, indicating device stability and lack of degradation.

Potential Advantages

Tegress Implant has several characteristics that may be viewed as advantages. Unlike collagen, Tegress does not require skin testing and has no demonstrated immediate or delayed antigenic concerns. Refrigeration is not required for Tegress, as it is with bovine collagen. Tegress can be implanted through a 25-gauge needle because of its low viscosity, as compared with the 23-gauge needle required by bovine collagen.

The overall implant volume of Tegress compared with that which remains long-term in the tissue is a 1:1 ratio, implying that there is essentially no loss of material after injection.

Medical, Inc., Irvine, CA) and is well known in urologic indications for use as a bladder irrigant, indicated for the symptomatic relief of interstitial cystitis.

Preclinical Data

Preclinical studies have shown the biologic safety of Tegress. In addition to demonstrating biocompatibility with ISO 10993-1 for permanent implants,

The overall implant volume of Tegress compared with that which remains long-term in the tissue is a 1:1 ratio, implying that there is essentially no loss of material after injection. In comparison, the ratio for bovine collagen is higher due to expected volume loss. This occurs because of reabsorption of buffered saline that accounts for approximately 66% of initial collagen

volume. This volume loss has been previously clinically managed by the tendency to overbulk with collagen. Tegress obviates the need for this injection nuance.

Results of the regulatory trial alluded to above are anxiously awaited, as the noted characteristics imply that Tegress may have clinical utility equal or even superior to currently available agents. The lack of antigenicity, stability of volume, and possibly improved durability (on the basis of in

improvement in I-QOL score by at least 50%. Safety monitoring included hematologic and serologic testing, urinalysis and urine culture determination, and recording and tracking of all complications and adverse events.

Study randomization criteria called for a 2-to-1 Tegress-to-collagen allocation schema. Women were allowed to receive up to 3 injections within the first 90 days. The relatively short window for injections was established in order to control the length of the

and without the need to observe visual coaptation at the completion of injection. Using these endpoint criteria, results with this agent have been intriguingly good.

A total of 253 women were randomized into the trial, 174 women receiving Tegress and 79 receiving collagen. Of this cohort, 16 of the Tegress-treated patients were initial “training cases” to familiarize the surgeon with the implanting nuances noted above. The analyzable trial population, therefore, consisted of 237 women; efficacy and safety analyses were performed on the 158 women who received Tegress. Although all patients were to be followed for efficacy and safety at 3, 6, and 12 months post implant, not all patients were available at each of these time periods due to various factors such as noncompliance and study withdrawal. Therefore, efficacy results were reported for the entire group and for the group known as the “consistent cohort”—patients for whom data were available at all study time periods. Preliminary outcomes analyses suggest superior performance for Tegress Implant versus the collagen control, evidencing higher dry rates and higher overall dry and improved rates on the most

Tegress possesses unique materials qualities, and as such, implantation of this device differs from that of collagen.

vivo studies) are all positive attributes associated with this device.

Tegress Clinical Trial

Study Design

The clinical trial that evaluated Tegress, and has now been completed, was a multicenter trial involving 15 sites in the United States and Canada. The study protocol included women with genuine SUI or stress-predominant, mixed symptoms. Patients could not have significant prolapse, were allowed to have had prior incontinence surgery (but not within 12 months), and were required to have specific urodynamic criteria (bladder capacity > 300 mL, no detrusor instability, and Valsalva leak point pressures < 100 cm H₂O).

The study assessed Tegress and compared it with bovine collagen for specific efficacy criteria, including change in Stamey grade, change in pad weight, and improvement in quality of life as assessed by the Incontinence Quality-of-Life (I-QOL) instrument. Patients were defined as improved after injection if they experienced: 1) an improvement of more than 1 in Stamey grade, 2) a decrease of $\geq 50\%$ in baseline pad weights on a 1-hour pad test, or, 3) an

trial, as all efficacy and safety data were to be reported with 12-month follow-up after the last injection.

Results

The mean age of the accrued population was 61 years, and the average duration of incontinence symptoms was 9.6 years. Close to half (46%) of the study cohort had had prior incontinence surgery,¹⁴ including anterior repairs, suspensions, and slings.

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this device differs from that of collagen. These implantation differences became apparent early in the clinical trial and necessitated slight procedural changes to obtain optimal material and tissue interaction. That is, experience with this agent suggested that optimal results were obtained with implantation in a more distal location within the urethra (approximately 2 cm distal to the bladder neck), with a slower rate of injection (60 seconds/implant site),

objective study endpoint of pad weight.¹⁵ The final study results will summarize the efficacy and tolerability of Tegress in the North American trial and are anticipated available for publication late in 2005.

Discussion

The use of urethral bulking agents continues to evolve. Although generally safe and efficacious, bovine collagen has been limited in utility

because of durability and antigenic concerns. Initial experience suggested 70% continence rates associated with collagen. More recent trials with collagen have shown that success to be split fairly evenly with moderate dry rates at 30%-40%, and an additional 30% of patients improved.^{16,17} Study of the new agent suggests considerably higher dry rates can be achieved.

Improvements in material science and expanding knowledge of host response to implanted materials have produced the development of bulking agents with reproducible tissue effects when implanted. The convenience of an outpatient procedure performed with local anesthesia, coupled with minimal post implantation convalescence and post injection voiding dysfunction, has further added to the interest in these materials. Ideally, the trend toward less implanted volume, no antigenic response, and greater durability within the host tissues is the goal of any new agent, as compared with bovine collagen. It is encouraging that Tegress fulfills these criteria. Evaluation of longer-term

experience with this material continues but initial results demonstrate the potential for increased rates of efficacy with Tegress Implant as a bulking agent for lower urinary tract indications. ■

References

- Voelker R. International group seeks to dispel incontinence "Taboo." *JAMA*. 1998;280:951-953.
- Dmochowski R. Advances in the treatment of stress urinary incontinence. *Rev Urol*. 2004; 6(suppl 5):S1.
- Estimated from 2000 US Census Bureau figures and incontinence prevalence data reported in Hampel C, Wienhold D, Benken N, et al. Definition of overactive bladder and epidemiology of urinary incontinence. *Urology*. 1997;50(S6A): 4-14.
- Hu TW, Waganer TH, Bentkover JD, et al. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology* 2004;63:461-465.
- Blaivas JG, Olsson CA. Stress incontinence: classification and surgical approach. *J Urol*. 1988;139:727-731.
- Appell RA, McGuire EJ, DeRidder PA, et al. Summary of effectiveness and safety in the prospective, open, multicenter investigation of collagen implant for incontinence due to intrinsic sphincteric deficiency in females [abstract]. *J Urol*. 1994;151:418.
- van Veggel L, Morrell M, Harris C, Dormans-Linssen M. A new device for the treatment of female stress urinary incontinence. *Proc Inst Mech Eng [H]*. 2003;217:317-321.
- Kershen RT, Dmochowski RR, Appell RA. Beyond collagen: injectable therapies for the treatment of female stress urinary incontinence in the new millennium. *Urol Clin North Am*. 2002;29: 559-574.
- Balmforth J, Cardozo LD. Trends toward less invasive treatment of female stress urinary incontinence. *Urology*. 2003;62(4 Suppl 1):52-60.
- Pannek J, Brands FH, Senge T. Particle migration after transurethral injection of carbon coated beads for stress urinary incontinence. *J Urol*. 2001;166:1350-1353.
- Kligman AM, Armstrong RC. Histologic response to intradermal Zyderm and Zypast (glutaraldehyde cross-linked) collagen in humans. *J Dermatol Surg Oncol*. 1986;12:351-357.
- Malizia AA, Reiman HM, Myers RP, et al. Migration and granulomatous reaction after periurethral injection of Polytef (Teflon). *JAMA*. 1984;251:3277-3279.
- Ritts RE. Particle migration after transurethral injection of carbon coated beads for stress urinary incontinence. *J Urol*. 2002;167:1804-1805.
- Dmochowski R, Herschorn S, Corcos J, et al. Multicenter randomized controlled study to evaluate Uryx® urethral bulking agents in treating female stress urinary incontinence. *Proc Int Continence Society (ICS)*, Heidelberg, 2002:187.
- Guttman C. Bulking agent showing durable SUI control at 1 year. *Urology Times*. July 1, 2004. Available at: <http://ut.adv100.com/urologytimes/articleDetails.jsp?id=105141>. Accessed: January 11, 2005.
- Corcos J, Fournier C. Periurethral collagen injection for the treatment of female stress urinary incontinence: 4-year follow-up results. *Urology*. 1999;54:815-818.
- Smith DN, Appell RA, Winters JC, Rackley RR. Collagen injection therapy for female intrinsic sphincter deficiency. *J Urol*. 1997;157:1275-1278.

Main Points

- Optimal bulking agents should be biocompatible, produce little or no immunogenic response in the host, and be stable on injection. Host-tissue response to the implanted agent should demonstrate minimal fibrosis, extracapsular inflammatory response, and resorption of injected material.
- The material, upon injection, should minimally deform the host tissues and not disrupt tissue planes.
- Ideally, a successful soft tissue bulking agent would be a single injection with permanent volume retention of the agent without migration, with partial or total incorporation into host lower urinary tract tissues.
- A clinical study assessed Tegress compared with bovine collagen for specific efficacy criteria, including change in Stamey grade, change in pad weight, and improvement in quality of life as assessed by the Incontinence Quality-of-Life (I-QOL) instrument. This study has now been completed and results will be forthcoming.
- Unlike collagen, Tegress does not require skin testing and has no demonstrated immediate or delayed antigenic concerns. In addition, refrigeration is not required for Tegress and it can be injected through a 25-gauge needle due to its low viscosity as compared with the 23-gauge size required by bovine collagen.
- Preliminary analyses suggest superior and lasting performance with higher overall dry and improved rates for Tegress versus the collagen control.