Update on Dermal Substitutes

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SUMMARY Tissue-engineered biological dressings offer promise in the treatment of burns, chronic ulcers, donor site and other surgical wounds, and a variety of dermatologic conditions. Despite this promise, cellular tissue-engineered products such as Dermagraft® and Apligraf® have suffered setbacks in recent years with a lower market share than the commercial promoters of these products anticipated. AlloDerm acellular dermal matrix, an older technology than these cell-based products, has made strong progress in winning over clinicians in various disciplines. Similarly, Integra Bilayer Matrix Wound Dressing (BMWD) continues to gain acceptance beyond its original burn audience. A review on the products is offered.

KEY WORDS: wound healing; burns; plastic and reconstructive surgery; tissue-engineering; artificial skin

INTRODUCTION

The term tissue-engineering has numerous definitions (1). However, a broad definition that can be formulated is “methods that promote biologic repair or regeneration of tissues and organs by providing signaling, structural, cellular or tissue elements”. The arsenal of tissue-engineering can include biomaterials, cells, growth factors and other signaling molecules, and in some instances engineering components such as pumps, tubes, bioreactors, and oxygenators.

Tissue-engineered biological dressings offer promise in the treatment of burns, chronic ulcers, donor site and other surgical wounds, and a variety of dermatologic conditions. Despite this promise, cellular tissue-engineered products such as Dermagraft® and Apligraf® have suffered setbacks and have not achieved the anticipated adoption by clinicians. Outside of the United States, complicated regulations for approval of products containing allogeneic cells, high pricing and challenges in obtaining reimbursement make the future of such products uncertain.

On the other hand, AlloDerm acellular dermal matrix, an older technology, has made strong progress in winning over clinicians in various disciplines. Similarly, Integra Bilayer Matrix Wound Dressing (BMWD) continues to gain acceptance beyond its original burn audience. In light of this, a review of the evolving uses of both of these acellular dermal replacement scaffolds is offered.

The need of dermal substitutes

The skin is the largest organ of the human body. It is the first line of defense against infection, prevents dehydration and helps regulate body temperature through changes in blood flow and sweat production. It is also a major sensory organ. The skin’s continuity and integrity can be compromised due to trauma, including surgery, or can become damaged secondary to an underlying pathology such as reduced venous or arterial circulation. Wounds can afflict only the epidermis (surface wounds) or can extend through the thicker dermal
layer (partial- or full-thickness wounds). Generally, the deeper the wound, the greater its biologic and clinical significance.

Skin consists of two distinct layers: the epidermis and the dermis. The thin epidermis comprises rapidly dividing keratinocytes, which produce keratin, a strong structural protein. The topmost layer of the epidermis is stratum corneum, a thin water-tight layer of dead, flattened cells. The thicker dermis, situated below the epidermis, is a complex association of fibroblasts and extracellular matrix, accounting for the skin’s mechanical integrity and elasticity. The skin’s blood vessels, nerve fibers and lymphatics all reside within this layer. The epidermis is nourished by diffusion of small molecules from the dermis. The skin’s appendages (i.e. hair follicles and sweat glands), traverse both levels. Beneath the dermis is the hypodermis, a loose connective tissue comprising primarily adipose tissue.

Wounds of different etiology, depth and surface area must be treated differently and have dissimilar clinical prognoses. Normal wound healing originates with regeneration from epidermal cells in the appendages of the deep dermal layer such as hair follicles. In-growth from wound edges also occurs but is ineffective for wounds larger than a few centimeters, and wound healing without a dermal layer results in contracture. It can be concluded that large or deep wounds and wounds that obliterate the skin’s appendages are of particular clinical challenge.

The ideal synthetic wound dressing or biologic skin substitute should have the following characteristics, enumerated for the most part by Pruitt and Levine more than twenty years ago (2), and added to by ourselves and others (3):

- absence of antigenicity
- tissue compatibility
- absence of local or systemic toxicity
- impermeability to exogenous microorganisms
- water vapor transmission similar to normal skin
- rapid and sustained adherence to wound surface
- conformity to surface irregularities
- elasticity to permit motion of underlying tissue
- resistance to linear and shear stresses
- tensile strength to resist fragmentation
- inhibition of wound surface flora and bacteria
- biodegradability (for permanent membranes)
- translucent properties to allow direct observation of healing
- reducing heal-time
- not increasing the rate of infection
- minimizing patient discomfort
- minimizing nursing care of wound
- patient acceptance
- low cost
- long shelf life, minimal storage requirements

Description and history of AlloDerm

AlloDerm® (AlloDerm® is a registered trademark of Lifecell Corporation, Branchburg, NJ) consists of a freeze-dried extracellular tissue matrix derived from donated cadaver skin, which, according to the manufacturer, is supplied by the US American Association of Tissue Banks-compliant tissue banks (4). AlloDerm is regarded by the Food and Drug Administration (FDA) as a minimally manipulated human tissue (5). “Minimal manipulation” is defined as processing that does not alter the characteristics of the tissue relating to its utility for reconstruction, repair, or replacement. Another criterion is “homologous use”, defined as the use of cellular or tissue-based products for the same basic function that it fulfills in its native state, at a location where such structural function normally occurs. As such, when used for the replacement of integumental tissue, AlloDerm does not require the filing and approval of a PMA or 510k, which is otherwise required of medical devices. However, if sold for a non-homologous use such as dural replacement, AlloDerm is regulated as a medical device and such filing and FDA approval would be required.

During the processing of AlloDerm, the epidermis and any cellular elements in the dermis are removed by exposure to a hypertonic solution, leaving behind a matrix of extracellular material including an intact basement membrane, collagen fibers, elastin filaments, and ground substance such as hyaluronic and proteoglycan. The integrity of the basement membrane complex, normal collagen bundle and banding patterns, and the absence of cellular material have been confirmed with electron microscopy (6). Importantly, the resulting matrix, which retains the essential biochemical and structural properties of human dermis, is non-antigenic (conventional skin allograft is ultimately rejected). The product is treated with detergent (0.5% SDS) to inactivate viruses and cryoprotectants (dextran, sucrose, raffinose and...
EDTA) prior to freeze-drying (7). AlloDerm is processed under aseptic conditions but there is no terminal sterilization, as both radiation and ethylene oxide would damage the matrix.

To use AlloDerm, it is aseptically removed from its foil packaging and placed in a saline bath. The manufacturer suggests that warming the saline to 37 °C but not above accelerates the process. The tissue should be submerged completely and soaked for five minutes or until the backing separates. After this, the AlloDerm is transferred to a second bath and soaked until it is fully hydrated, as evidenced by its being soft and pliable. This can take up to 40 minutes for thicker pieces. The graft should be used within four hours of preparation. When used for grafting, it should be placed with the dermal side down (smooth and shiny) and basement membrane side up (rough and dull) (8).

When placed in a wound, AlloDerm is populated by circulating cells, which establish a neovascularure and elaborate new extracellular matrix while incorporating the AlloDerm material. The graft is ultimately remodeled into the tissue with characteristics of the site into which it has been implanted (9). However, having no epidermal layer, it provides a limited barrier function. When used as a graft, it must be dressed with a thin autograft as well as moisture-retaining dressings.

AlloDerm is readily available and has a shelf life of two years under refrigeration. It is available in a variety of configurations, ranging from 2 to 72 cm² in area and 0.17 mm to 1.8 mm (and up) in thickness (10).

When the famous bank robber Willie Sutton was asked why he robbed banks, he simply replied: “Because that’s where the money is” (11). It is not surprising then that the earliest focus for AlloDerm and other tissue-engineered skin products was in burns. It was thought that it was where the skin was needed. Although the most obvious of uses, it is also the smallest of contemplated applications today.

The commercialization of AlloDerm as a dermal replacement in the grafting of full-thickness and deep partial-thickness burns began in December 1993. Since 1995 it has also been used in periodontal surgery and reconstructive plastic surgery. The acellular matrix is also sold under the brand names Repliciform® and Graftjacket® for urologic and orthopedic procedures, respectively. It is also available in a micronized form for injection termed Cymetra®. Repliciform, Graftjacket and Cymetra are beyond the scope of this article.

A review of clinical applications

**AlloDerm in burns**

Each year in the United States, 696,000 people visit the emergency room due to burns (12), resulting in 50,000 hospitalizations (13). The majority of these cases, those in which the burns are not extensive, do not pose a clinical challenge. These patients usually have sufficient healthy skin from which autograft can be harvested.

However, sometimes sufficient healthy material is unavailable for autograft or the added trauma of creating a donor wound cannot be tolerated. According to the American Burn Association (14), the average size of a burn injury admitted to a burn center is about 14% of total body surface area (TBSA). Burns of 10% TBSA or less account for 54% of cases, while burns of 60% TBSA or greater account for just four percent of admissions.

The subset of severely injured patients represents the most compelling application in burns for tissue-engineered products. There also are certain rare skin disorders such as toxic epidermal necrolysis (TEN) and epidermolysis bullosa (EB), in which conditions resemble those that result from severe burns. These too may benefit from the application of tissue-engineered biologic dressings. For example, AlloDerm and ultrathin epidermal graft have been used in a case of purpura fulminans, a syndrome of intravascular thrombosis of the skin with hemorrhagic infarction (15).

Deep partial-thickness and full-thickness burns typically require autografting to achieve healing. In severe burns, a temporary covering is often employed as a bridge to autografting. Allograft from cadaver skin has been the traditional choice, providing biologic closure, reduction in pain and decreased fluid loss. The immune suppression observed in severely burned patients prevents rapid rejection of allograft but rejection ultimately occurs, typically within days to weeks, necessitating repeat allografting if the patient is not yet ready for autografting. The advantages of allograft are tempered by variable supply, the possibility of disease transmission, although careful screening of donors substantially reduces this risk, and bleeding provoked upon removal. Porcine xenograft such as E-Z Derm (Brennen Medical, St. Paul, Minnesota) is sometimes used as a temporary wound covering. It provides similar benefits as allograft but is rejected or “ejected” more rapidly (16).

Yet, AlloDerm is not considered a replacement for allograft as a temporary dressing. Rather, it is a permanent dermal replacement facilitating...
thinner autografts (17,18) with a resultant decrease in donor site morbidity. In many applications, limited autograft availability necessitates maximizing the available resource in the form of thinner grafts in which donor sites can be reharvested sooner, meshing of the graft and using cultured epidermal cells. If the method chosen (e.g., a very thin split thickness skin graft) does not supply a solid dermal layer, wound contraction, scarring and long-term disability can result.

Under best of circumstances autografting creates a donor site, which is itself a site of potential infection and fluid loss. The donor site is generally a partial-thickness wound, but sometimes it extends no deeper than the epithelium. Donor wounds are associated with pain, discomfort, fluid collection and the ever-present possibility of infection. Being able to take a thinner autograft reduces donor site wounds, leads to more rapid donor site healing, and enables more rapid donor site re-cropping procedures. This can ultimately result in a reduced length of hospital stay and more rapid patient rehabilitation.

As with any graft, the wound bed must be prepared appropriately prior to AlloDerm placement. This means a clean, viable, vascularized tissue with adequate hemostasis. In the case of severe burns, this can mean debridement to muscular fascia. If there remains even a small amount of bleeding, the AlloDerm should be meshed, as should the overlying autograft (8).

AlloDerm is often used as a dermal layer in the grafting of major joints, where it helps prevent scar contracture. Contractures are associated with the loss of limb mobility and often necessitate reconstructive surgery. Two case studies in burns have been first reported by Wainright (6). In a 67-patient study in full-thickness or deep partial-thickness burns, AlloDerm plus a thin split thickness skin graft (STSG) was deemed equivalent to a thicker split thickness skin graft used alone, in a within patient design (19). In a report on three patients with full-thickness burns of distal extremities, Lattari et al. report on the use of AlloDerm with ultrathin autograft with “good to excellent” results in the range of motion, grip strength and fine motor coordination (17). In a study of six children, ten burn sites were grafted with AlloDerm and thin autograft, and ten matched sites on each patient were grafted with a thicker autograft. There were no significant differences between the two procedures as gauged by epithelialization and the Vancouver Scar Scale (17). At follow-up at a mean of 43.7 weeks, there was still no difference in the Vancouver Scar Scale score between the two procedures (21).

The ability to harvest a very thin autograft is particularly important in the elderly, in which harvesting the donor site often creates a new full-thickness defect due to thinness of the underlying skin, often discouraging operative wound debridement and autografting in this population. In a study (18) comparing 10 elderly burn patients receiving Alloderm with historic control, the donor site healing time was substantially reduced with Alloderm (12 days vs. 18 days), while graft take was the same in the two groups. However, the use of AlloDerm did not result in improved mortality.

**AlloDerm in reconstructive surgery**

Today, AlloDerm is by far more frequently used in reconstructive surgery than in burns, typically as a soft tissue implant, most commonly in skin cancer excision, scar revision, oral resurfacing, cleft palate repair, oculoplasty, revision rhinoplasty, and septal perforation repair (22). As each procedure is different, the literature is often scant on any particular use. Many of these procedures can also be performed using autograft, xenograft or synthetic alloplastic materials. In cases where autograft can be harvested in sufficient amounts and without undue trauma to the patient, it is often preferred. Fat, dermis, fascia, cartilage, bone, and muscle are all used. In many cases, however, the available autograft is insufficient or the scarring and donor site trauma are unacceptable. Alloplastic materials suffer from poor tissue adherence, elicit a foreign body reaction, and are at risk of extrusion (23). Xenograft bovine collagen is often used as well. However, the material is rapidly resorbed and is antigenic in some individuals.

**AlloDerm in head and neck surgery**

In one series, 13 of 17 patients with symptomatic anterior nasal septal perforations that had failed conservative treatment had a successful repair of the perforation with a closed endoscopic repair using AlloDerm and an anteriorly based inferior turbinate flap (22). In primary cases of septal perforation, the avoidance of a donor site, which is usually necessary to harvest temporalis fascia or pericranium, is a notable advantage. In a series of 12 patients receiving AlloDerm as an interpositional graft for repair of a nasal septal perforation, 11 of 12 had successful outcomes with complete closure of the perforation (24). AlloDerm has been successfully used for nasal contouring but was limited by partial absorption in some patients and induration of the graft area (25). In three patients with unilateral partial or full-thickness nasal septal...
mucosal defects, AlloDerm was used with excellent results reported at two-month follow up (26). AlloDerm has also been reported to perform well at two-year follow up when used to correct dorsal nasal irregularities that occurred postoperatively, such as thinning of the nasal skin, bony irregularities and adhesion of dorsal skin to bone (27). AlloDerm use in conjunction with a high density polyethylene implant has been described in a major saddle nose deformity when sufficient autograft is unavailable (28).

AlloDerm has been described as “an ideal material for closure of skull base defects” eliminating the need of an autogeneic graft and donor site (29). Nine of nine cerebrospinal fluid leaks were successfully repaired as were 22 of 24 sellar repairs after trans-sphenoidal hypophysectomy. Importantly for head and neck oncologic surgery, graft thickness and neovascularization are not adversely affected by prior external beam radiation, as demonstrated in a rat study (30). Even direct external beam radiation of AlloDerm has relatively modest effects, hindering recellularization in the early post-treatment period but normalizing by 12 weeks (31). Neovascularization, however, remained reduced in the irradiated group even at 12 weeks, but without effect on ultimate graft survival.

AlloDerm is considered a good alternative to temporalis fascia, the gold standard, in tympanoplasty when no temporalis fascia can be located (e.g., revisions) or when it is desirable to avoid a separate donor site during transcanal approach (32). In a retrospective analysis comparing 20 patients receiving AlloDerm with 20 patients receiving temporalis fascia for tympanic grafting, there were no graft failures in either group and no statistically significant between group difference in residual conductive hearing loss (33). In a series of 24 patients, 17 with simple perforations and seven with chronic otitis media with cholesteatoma, the success rate with AlloDerm in achieving closure of the tympanic membrane was 87.5%, equivalent to that of temporal fascia, in the opinion of the author (34). In seven patients with traumatic perforations of the tympanic membrane that failed to close spontaneously, AlloDerm was placed over the defect as an in-office procedure. Six of seven patients experienced complete healing and an improvement in hearing (35). Similarly, when sufficient mastoid fascia is unavailable, AlloDerm has been used to cover mastoid defects created by canal wall down mastoidectomy, a procedure used to address cholesteatoma or chronic ear disease.

The creation of a dry, well-epithelialized mastoid bowl is cited as one of the challenges in this procedure (36).

In a 30-patient controlled clinical study, AlloDerm was used as an interpositional barrier to reduce the incidence of Frey’s syndrome following superficial parotidectomy (37). In a similar 64-patient study, AlloDerm as an interpositional barrier reduced the subjective (3.1% vs. 9.3%) and objective (0% vs. 40%) incidence of Frey’s disease, but carried a higher risk of complication (9% vs. 25%), notably seroma formation (38).

In a seven-patient series, AlloDerm has been deemed effective for repair of wide clefts of the soft and hard palate when applied deep to the oral mucosa (39). It was also used in 10 patients to reconstruct large pharyngeal defects in which primary closure was not possible. Functional results were deemed excellent, although two patients developed fistulas that resolved with conservative management (40).

AlloDerm has been used on the donor site created by the harvest of a radial forearm free flap, a preferred tissue source for head and neck reconstruction. Partial graft loss with exposure of flexor tendons is a common complication. In a retrospective chart review comparing AlloDerm to split-thickness skin graft from the thigh, AlloDerm treated patients required considerably longer healing time than those undergoing skin grafting (12-16 weeks vs. 4-6 weeks) (41). In a 52-patient study, AlloDerm was used in place of split thickness skin grafting for radial forearm free flap coverage. Full range of hand motion was possible in three days, but complete healing took 8 to 12 weeks. Contracture was minimal and the only complication was seroma formation in five patients (42).

The use of AlloDerm has been reported in 11 patients for augmentation of soft-tissue defects or scarring of the face, where it was deemed an “excellent augmentation material” and was without significant complications (43). In a report on 12 patients receiving AlloDerm for lip augmentation, all were pleased with their results at an average follow up of seven months (44). Initial induration eventually subsided and the graft was reported to take on a natural feel. Rolled up like a cigarette, AlloDerm has been used for lip augmentation with “extreme satisfaction” expressed by the patient (45). AlloDerm in combination with fat autograft has been reported to yield superior results to fat autograft alone when used for lip augmentation (46).
AlloDerm has also been reported in one case to repair a depressed tracheostomy scar with a tracheal tug (47), and in another to avoid a depressed tracheostomy scar (48). A case study has been reported describing its use in reconstructing a calcaneal defect, along with full-thickness skin grafting at a later stage (48).

**AlloDerm in neurosurgery**

AlloDerm has been used in various types of neurosurgical reconstruction (36,49), often as a dural substitute (49-51), typically when sufficient temporalis fascia is unavailable, reportedly with good results. It has even been used for in utero repair of myelomeningocele (53). The product cannot be promoted as a dural substitute by LifeCell (54) as such a use would require regulation as a medical device and not banked human tissue.

**AlloDerm in ophthalmic surgery**

In 21 procedures, thick AlloDerm grafts were deemed comparable to hard palate grafts in posterior and middle lamellae reconstruction to correct lower eyelid retraction, as compared with historic control (55). In a separate 19 graft study, AlloDerm, when used as a spacer graft in lower eyelid surgery, contracted significantly more than hard palate mucosa autograft (57%) vs. 16%) but was still associated with a high rate of clinical success, except when used for a mildly contracted socket, in which only two of five had adequate results (56). A retrospective review has been published of 105 cases of AlloDerm use in 63 patients for various ophthalmic and reconstructive procedures, primarily as a posterior lamellar conjunctival spacer graft in the lower lid (92 cases), but also as upper eyelid posterior lamellar conjunctival spacer graft (4 cases), lower eyelid conjunctival spacer graft in anophthalmic contracted socket (2 cases), and as a soft tissue interpositional graft (5 cases) (57). All 105 cases were reported to exhibit improvement following the procedure with no complications attributable to AlloDerm. A retrospective 23-patient series similarly concluded that AlloDerm was an “excellent barrier and reconstructive grafting material” when used in a variety of ophthalmic plastic applications (58).

Looking forward in this indication, autogeneic conjunctival keratinocytes were recently grown on AlloDerm in a serum-free system, offering the promise of an implant sufficiently rigid for eyelid reconstruction with the addition of a conjunctival layer to minimize mucosal irritation (59).

**AlloDerm in general reconstructive procedures and complex hernia repair**

AlloDerm has been used successfully as the base for a latissimus dorsi flap in a complex chest wall defect in a 61-year-old woman following resection of a sarcoma leaving a 20 cm x 20 cm soft tissue defect (60). It has been used to repair various breast implant-related complications, notably capsular thinning and implant rippling, with mostly good results (61). It has been indicated by some that AlloDerm and cultured epidermal autograft are preferred for the coverage of aplasia cutis congenital (62).

AlloDerm has recently become popular for complex hernia repair (9,63,64). In fact, Lifecell reports that the 64% growth in AlloDerm use in 2004 versus 2002 was primarily driven by its use in this indication (65). The success of one author in early studies led him to adopt AlloDerm in all subsequent abdominal wall and breast reconstruction repairs (9). In a report on 44 patients receiving AlloDerm for complicated incisional hernia repair or transverse rectus abdominis musculocutaneous (TRAM) flap surgery, all were alive with no clinical infection or reports of bowel obstruction or fistula at a mean follow up of 20 months. Two patients developed seromas, three experienced postoperative infections, and two had wound dehiscence.

An additional benefit to the use of AlloDerm in this application may be reduced adhesion formation as compared with polypropylene mesh alone (66) or Gore-Tex, as demonstrated in animal models (67). It is reported to perform as effectively as Gore-Tex in mechanical strength at one month in a rabbit ventral hernia model and to become well vascularized in that interval (67). It has also been used in conjunction with fibrin glue, in the context of a peritoneal cavity left open for controlling fulminant intra-abdominal sepsis, to patch intestinal deserosalizations (n=2) and to close an intestinal fistula (n=1) (68). It is thought to be more resistant to infection than a prosthetic material (9).

**AlloDerm – summary and conclusion**

AlloDerm offers several advantages for soft tissue augmentation in dermatology, dermatosurgery, and plastic and reconstructive surgery. It is non-antigenic, integrates quickly into the patient’s own tissue, is available off-the-shelf and allows for a thinner donor-site wound. It is relatively resistant to infection as compared with synthetic materials, and has been used successfully in contaminated environments (69). It is pliable and has attractive handling characteristics.
Absorption of the product is its largest liability (56,70). Ten volunteers participated in a study comparing AlloDerm with Zyplast (INAMED Aesthetics, Santa Barbara, California), a gluteraldehyde cross-linked bovine injectable type I collagen. Each subject had both materials implanted, one behind either ear. About 20% of AlloDerm was noted to remain at six-month follow up, as determined by digital photographic analysis of the surface area and lateral projection of the implant. This residual amount remained stable at 12-month follow up, whereas Zyplast was completely resorbed by six months (71,72).

Absorption, particularly in plastic and reconstructive procedures, must be anticipated and corrected for in advance to avoid a cosmetically undesirable outcome. This requires a certain amount of guesswork by the surgeon as to how much of the implanted material will remain. In 58 patients receiving AlloDerm for nasal contouring, 45% showed signs of greater than 50% absorption. This can result in under-correction of the deformity if the surgeon does not compensate for it. However, in 20 patients followed for two or more years, AlloDerm was noted to be stable between years one and two. This indicates that if the initial absorption can be corrected for at the time of surgery by implanting extra material, stable results can still be achieved (25). Similarly, a possible 15%-20% shrinkage, which remained stable after 4-6 weeks, has been reported when AlloDerm is used for lip augmentation (44). Rolled or stacked AlloDerm is specifically noted to have unpredictable absorption (59). But certainly not all clinical investigators have been troubled by this problem (27), particularly in the short term (46).

One potential disadvantage in grafting is AlloDerm’s lack of epidermis. The removal of this layer during processing is necessary since the epidermal cells are antigenic and stimulate rejection. The lack of “traditional epidermis” requires additional wound closure, typically achieved with a thin autograft. However, for large wounds, or cases in which the use of autograft is not possible or desired, other temporary dressing can be used to close the wound.

It is important to inform the patient prior to surgery of the source of the transplanted material. Some patients may be “repulsed” by the thought of cadaveric tissue being implanted into their bodies (73). In a survey of religious leaders in the United Kingdom, 77% thought that prior to use patients should be informed of the constituents of a biological product, and that informed consent should be obtained (74).

The product is fairly expensive at £5.90 per sq. cm (75). Driving the cost of the product is its inherent reliance on human tissue, aseptic processing and the inability to perform terminal sterilization without compromising the integrity of the product’s matrix.

AlloDerm is human tissue and the risk of disease transmission, particularly prion-related illnesses such Creutzfeldt-Jacob (CJD) disease, cannot be said to be zero. To our knowledge there have been no known cases of transmissible infection with AlloDerm. The manufacturer adheres to strict donor acceptance criteria, maintains careful records, and follows the guidelines of the American Association of Tissue Banks. Further limiting risk, the donor skin processed into AlloDerm is not pooled. The risk of CJD transmission with non-neurological tissue such as skin is believed to be quite low.

In the future, AlloDerm may be utilized as a scaffold for the growth of cells to generate living tissue-engineered products (76,77). However, it is reported that cells proliferate mainly on the surface of AlloDerm and do not penetrate the interior as well as on a synthetic matrix (76). The addition of an epithelial layer to obviate the need for a thin autograft would be a notable advance. This approach has already been taken to produce conjunctiva and an oral mucosa equivalent (59,78). Unfortunately, it is doubtful that the additional cost of these potential improvements could be borne commercially.

It is possible that eventually the same process used to render human cadaver skin non-antigenic can be applied successfully to porcine tissue, in a fashion allowing terminal sterilization. This would dramatically increase supply, drop costs, and potentially expand the uses of dermal substitute. In recent animal studies using a porcine acellular dermal matrix (processed differently from AlloDerm), a robust immune response was observed with generally poor wound healing and significant contracture (79,80). New processing technologies will need to be developed to extend the success of AlloDerm to xenogeneic tissue.

Integra Bilayer Matrix Wound Dressing – History and Description

Integra Bilayer Matrix Wound Dressing (BMWD) is a two-layer membrane consisting of a cross-linked bovine collagen/shark chondroitin-6-sulfate
layer, intended to mimic dermis, and an occlusive silicone outer layer which temporarily provides the sealant properties of epidermis. The pore size of the collagen sponge dermal equivalent layer, at 70-200 microns, is intended to promote cell migration. The collagen layer, after being placed on the wound, is infiltrated by fibroblasts that begin to lay down extracellular matrix and remodel the existing collagen. Over three to six weeks this layer takes on characteristics of true vascularized dermis (81). The synthetic outer layer is ultimately removed and replaced with a split thickness skin graft (STSG), as thin as 0.005 (82) or 0.006 inches in depth (83). Fang et al. found it impossible to harvest useful grafts of less than 0.005 inches (83).

Integra BMWD was developed in 1980 (84) at Harvard Medical School and Massachusetts Institute of Technology, and subsequently licensed to Marion Laboratories Company. In 1990 the license was acquired by Integra Life Sciences Corp. (Plainsboro, New Jersey). In March 1996, the product was approved by the FDA for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient (85). The label was subsequently expanded, based on retrospective studies, to include “the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds” (85). Today, the device is widely used in burn surgery, including chemical (86,87) and electrical (86) injuries, and plastic and reconstructive applications.

Integra BMWD has a shelf life at room temperature of two years, is available in a number of sizes, and is moderately expensive at £3.32 per sq. cm (75). BMWD appears to be well tolerated by the body and does not elicit rejection reaction (88) or significant inflammation (89).

**Review of clinical applications**

**Integra BMWD in burns**

Integra BMWD was initially reported in 1981 to have been successfully applied to a series of ten patients with full-thickness burns over 50%-90% of body surface area (90). By 1987 the product had been used in over 200 cases, in which it performed similarly to autograft in closing postexcision burn wounds (91). In the 149-subject pivotal clinical trial, in which BMWD and conventional care (either autograft, allograft, xenograft, or synthetic wound covers) were assigned to matched-pair sites on patients with full-thickness thermal injuries, the median take of BMWD was less than that of conventional autograft (80% vs. 95%) (92). These results were considered acceptable by clinical investigators when consideration was given to overall management of the burn patient and the immediate availability of BMWD. The use of BMWD was associated with less hypertrophic scarring and greater patient satisfaction. At six year follow up, BMWD retained its function and cosmetic appearance (91). However, Integra BMWD can be complex to use and the learning curve can be substantial. Not all early experiences with the product were positive (93).

Retrospective analysis of patients with massive burn injuries treated at Massachusetts General Hospital over a 12-year period, from 1974 to 1986, suggests that the introduction of BMWD resulted in improved survival (94). But in a subsequent retrospective analysis at Massachusetts General Hospital of 270 adult burn patients with greater than 20% TBSA involvement treated between 1992 and 2000, Integra BMWD had no effect on mortality. It did result in decreased hospital length of stay in the subgroup of patients with two or more mortality risk factors (63 days vs. 107 days), but statistical analysis is hindered by the historical nature of the study (95). A post-approval 216-patient, multicenter clinical trial in burn patients (mean TBSA 36.5%) was conducted to further study the rate of infection with Integra BMWD (86). The mean and median take of Integra BMWD was 76.2% and 95%, respectively. The mean take of epidermal autograft was 87.7% with a median of 98%. This was superior to that seen in the 149-patient pivotal trial (92), possibly due to adherence to the principles of complete excision and hemostasis prior to Integra BMWD placement. Importantly, the rate of superficial and invasive infection was 13.2% and 3.1%, respectively.

BMWD has been used to close acute thermal injuries to the hand and for hand reconstructive procedures (96). Acute grafting was performed on 15 hands (11 patients) with 100% take. At follow up (median of 12 month) the resulting skin was deemed flexible and supple without adherence to the deeper structures, allowing for good functional recovery. Cosmetic results were considered satisfactory by both the patients and physicians. In re-
constructive procedures on 14 hands (11 patients) significant improvements were achieved on the Vancouver Scar Scale and in several measures of hand function.

Serial surveys of 15 German burn centers conducted in 1999, 2001 and 2003 suggest that the indications for Integra BMWD in burns has narrowed over the years to full-thickness burns of greater than 50%-60% TBSA, in other words, to those patients in which primary wound closure cannot be achieved with split-thickness skin grafting in the immediate post-injury period (97). Four of 15 centers had not used the product in the past two years due to high costs, uncertain outcomes, and the complicated and intensive care required in the interval between BMWD placement and split-thickness skin grafting.

Adverse events reported in the pivotal clinical trial (92) included wound fluid accumulation, positive wound culture and clinical wound infection. The use of BMWD was associated with a higher rate of infected wound sites than the use of autograft, resulting in these cases in partial or complete loss of take. Other possible complications include shearing of the BMWD after application, graft loss, hematoma, silicone layer detachment, and incomplete epidermal graft take (98).

Careful attention to the wound during several weeks prior to STSG is therefore essential. The use of vacuum assisted closure in eight patients with complex wounds has recently been reported to result in accelerated vascularization of BMWD, an improved rate of take and therefore earlier skin grafting as compared to prior published results (99). This is consistent with a 12-patient randomized clinical trial comparing Integra BMWD alone (including negative-pressure preconditioning) with BMWD plus fibrin glue and negative-pressure therapy. Combination treatment resulted in an increased take (98% vs. 78%) and decreased time to skin grafting (10 days vs. 24 days) (100).

**Integra BMWD for plastic and reconstructive procedures**

In recent years BMWD has been more often used for plastic and reconstructive procedures where it enables coverage of large areas, resists contracture, promotes granulation and facilitates delayed autografting, even over avascular areas such as tendon, bone and cartilage. Importantly, BMWD does not adhere to these structures (98,101). In 23 elderly patients with scalp defects with exposed bone following cancer resection, Integra BMWD was applied under local anesthetic followed by delayed skin grafting at an average time of 30 days (102). All patients achieved a closed wound with no evidence of exposed bone. However, infection complicated 21.7% of cases, necessitating replacement of the BMWD.

In two reported cases, Integra BMWD was used to close a wound in an irradiated scalp, an environment challenging due to impaired wound healing and compromised vasculature (103). The authors theorize that the ability of BMWD to vascularize over several weeks enabled it to succeed where a skin graft, requiring vascularization within 48-72 hours of placement, would probably have failed.

A case study describing its use in immediate coverage of a large avulsion injury, followed by skin grafting, has been described (104), as well as successful resurfacing of a lower extremity following a latissimus dorsi free flap that had become unstable (105). It was used to cover a radial artery adipofascial free flap to the lower extremity, followed by delayed skin grafting, with good cosmetic outcome (106). Its successful use following cancer resection to cover nasal wounds with exposed cartilage, followed by split thickness skin grafting, has been reported in three case studies (107). Integra BMWD has been used in the challenging application of closing a radial forearm flap donor site over exposed tendon with take occurring in nine of ten cases (108). A case study has been reported describing its use to close a forehead donor wound (109), a site that typically yields significant contour deformity. The authors concluded that the resultant appearance was a significant improvement over the likely outcome of STSG applied directly to the peristeum.

It was used in conjunction with STSG for closing the wound created by excision of giant hairy nevi in four pediatric patients (98); in conjunction with cultured autologous epithelium to cover the wound resulting from excision of a giant nevus on the back in a boy with neurocutaneous melanosis (110); and to achieve wound closure with STSG following excision of a giant congenital melanocytic nevi covering the entire back of an adult patient (111).

Release of post-burn injury contracture is another area where BMWD is often used. Retrospective evaluation of BMWD in 89 consecutive patients (127 contracture release procedures) indicated that at 76% of the release sites, the range of motion or function was rated by physicians as good or excellent. Patients expressed satisfaction
with the procedure at 82% of the sites. Seventy-five percent of the sites were free from contracture recurrence during follow up (mean of 11.4 months) (112). As in prior studies, the most significant complication observed with the use of BMWD was infection or microbial colonization (20%), followed by fluid accumulation under the silicone layer (14%).

In a series of 10 pediatric patients with upper extremity contractures reconstructed with BMWD, only six had an excellent outcome, whereas four had poor results (113). This was attributed by the authors to non-compliance with splinting on the part of the patients, highlighting the importance of postoperative care in this population.

In a series of 12 patients undergoing breast reconstruction and contracture release, the use of Integra BMWD plus a very thin (0.005 in.) epidermal autograft resulted in durable improvement in breast contour and shape without clinically significant contracture within the follow up period (12 months) (82). Ninety-two percent of patients expressed a high degree of satisfaction with the outcome.

In 29 evaluable patients (37 wound sites) receiving Integra BMWD for various reconstructive applications, mostly burn scar revision, good results were achieved at 26 sites, average results at six, and poor results in three instances. The infection rate in this series was 12.8% (101). Using Integra BMWD to close the wound, thirteen patients with prior burn injuries had successful contracture release of the upper extremity with no case of infection (114).

In the challenging indication of anterior neck contracture, Integra BMWD was initially successful in five patients but contracture recurrence of greater than 50% occurred in all cases (115). This was attributed by the authors to the difficulty in achieving immobilization in this area. Successful use in neck contracture in a child has been reported (116), but follow up for reconstructive care has not been published.

It has been pointed out that in reconstructive procedures full vascularization of the neodermis takes four weeks and that STSG prior to this can result in delayed graft take (117). This is in contrast to the results in acute burns which indicate that vascularization of the BMWD is completed by two weeks (81). In fact, grafting beyond two weeks in burn patients is thought by some to contribute to over-granulation (115). Clinical examination of matrix color has been shown to correlate with the degree of vascularization (117), guiding clinical decision making.

**Integra BMWD in other skin disorders**

Integra BMWD is useful in a variety of blistering, ulcerative, and purpuric disorders. Its use has been described in challenging chronic foot ulcers in two cases of Werner’s syndrome, a premature aging disorder (118); to reconstruct a large defect following excision of a squamous cell carcinoma in a patient with dystrophic epidermolysis bullosa (119); and to cover amputation sites in a case of purpura fulminans (120), a rapidly progressive hemorrhagic necrosis of the skin.

**Integra BMWD – future directions**

The developers of BMWD pointed out themselves that one drawback of the product is its lack of permanent epidermal layer, ultimately necessitating an autograft, albeit a thin one (121). Seeding the bilayer membrane with autologous or heterologous epithelial cells before grafting is one alternative (122), as is sequential use of Integra BMWD and cultured cells. The consecutive use of Integra BMWD and cultured epidermal autograft (CEA) has been described in three patients, yielding 98% engraftment (123). A patient with 93% TBSA burn was treated with a combination of Integra BMWD, split-thickness skin graft and CEA (124), as was a 15-year-old with 60% TBSA burns (125).

In a pig wound healing model, cultured autologous keratinocytes applied either to the underside of Integra BMWD or directly to the wound bed resulted in upward migration of keratinocytes through the matrix, yielding confluent surface epithelium, but seeding onto the matrix was deemed more efficient (126). A novel approach uses a fibrin-based autologous cultured epithelium grafted onto the BMWD (127). This cultured epithelial construct is reported to have better handling characteristics than those not cultured on fibrin. The addition of autologous cultured fibroblasts has also been described in one patient with 76% TBSA (128). In this case the use of BMWD in conjunction with autologous fibroblasts, keratinocyte sheets and 1:6 expanded skin grafts has been reported to provide best results in this patient as compared to any other combination of these modalities. Cultured epidermal autograft has also been grown on fibroblast-seeded Laserskin (Fidia Advanced Biopolymers, Italy), a thin hyaluronic acid membrane that has been laser-perforated with microholes to facilitate ingrowth and proliferation of cells. This construct, termed Composite Biocompatible Skin Graft by its inventors, was grafted onto Integra BMWD in three patients with take ranging from 50 to 100 percent (129,130).
The addition of adnexal structures, notably hair follicles, to the Integra BMWD has been described in a patient with a large scalp burn (131). The regenerated epidermis in this case was derived from stem cells in the hair follicle, but a sheet of autologous cultured keratinocytes was still required to achieve closure.

Despite the promise of cellular constructs based on or in conjunction with BMWD, the acceleration of healing observed by combining BMWD with negative pressure, as described above, will likely lower the impetus to pursue cellular modalities commercially.

**Integra BMWD – summary and conclusion**

Integra BMWD has proven useful in a wide variety of burn injury, plastic and reconstructive procedures. It is readily available, stable to storage, well-tolerated and does not elicit a rejection reaction. The use of the product is generally thought to result in superior skin cosmesis but not to the point of being equivalent to normal skin. Reduced donor site morbidity, a thinner STSG, faster donor site healing, and ability to re-crop donor site more often are important advantages.

The downsides of the product are notably wound fluid accumulation, positive wound culture and clinical wound infection, leading in some cases to graft failure. The necessity for a second procedure (STSG) to definitively close the wound is a significant drawback, necessitating careful wound care in the several-week interim, a period fraught with opportunities for complications and graft failure. This, coupled with costs, has led some to abandon the product as noted above.

Although Integra BMWD plus cultured epithelial autograft offers promise to ameliorate some of these problems, the high cost and logistical complexity of this combined procedure are likely to limit its adoption. The incorporation of signaling peptides, such as RGD, or small molecule chemical mediators to accelerate Integra BMWD vascularization enabling more rapid STSG is one possible direction for improvement. In the near-term the most promising improvement to Integra BMWD appears to be the addition of fibrin glue and negative pressure to accelerate take.

**CONCLUSION**

Both AlloDerm and Integra BMWD are members of the small family of commercially available dermal substitutes, which provide a three-dimensional matrix to promote tissue regeneration, neo-vascularization, host cell colonization and accelerated healing. Both products are designed to deter wound contraction, which is a natural mechanism to reduce wound surface. This, otherwise, leads to scarring, poor cosmetics and impaired function. Integra BMWD also provides wound closure through its occlusive silicone layer.

Although these products do not fulfill all of the requirements for an ideal skin substitute, they both have important applications in cases of severe skin loss such as burns or large and deep wounds, and in other situations in which gold standards such as surgical wound closure (healing by primary intention) or autografting are not practical. Research and clinical development will likely yield new products and, by eliminating deficiencies, improve upon the existing ones. This gives hope to patients and physicians for continued improvements in functional and cosmetic outcomes.

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