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Comparison of two cadaveric acellular dermal matrices for immediate breast reconstruction: A prospective randomized trial☆

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Outcomes

Summary AlloDerm RTU® and AlloMaxTM are two acellular dermal matrices (ADMs) used in implant-based breast reconstruction. In this study, we examined whether different processing methods for the ADMs lead to a disparity in histologic, clinical, and financial outcomes after breast reconstruction. Thirty patients undergoing implant-based breast reconstruction were randomized into AlloMax or AlloDerm arms (n = 15, each). ADM was placed at the time of immediate reconstruction. Patients were evaluated for complications on postoperative days 7, 14, and 30. During implant exchange, ADM biopsies were taken and compared histologically for vascular and cellular infiltration. Patient satisfaction was evaluated using the BRECON-31 questionnaire 1 year after implant exchange. A cost analysis was performed comparing the two ADMs. Patient demographics and complication rates were similar between the two groups ($p > 0.05$). Histologically, vessel density and fibroblast/inflammatory cell infiltrate were greater on the dermal side than on the implant side ($p < 0.01$) in both ADMs, suggesting greater vascular and cellular in-growth from the dermal side. Vessel density in the middle portion of the Allomax biopsies was significantly higher than the same site in the Alloderm biopsies ($p < 0.05$). The extent of fibroblast/inflammatory cell infiltration was similar in both arms ($p > 0.05$). The BRECON-31 satisfaction questionnaire yielded similar responses across all metrics between the two study arms. The negotiated price was slightly different when comparing

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the two ADMs, with no significant difference in ADM reimbursement. In this study, AlloDerm RTU and AlloMax were successfully used for implant-based breast reconstruction with comparable outcomes.

Introduction

Implant-based breast reconstruction accounts for 73% of the over 102,000 breast reconstructive procedures performed annually in the United States.[1] Unfortunately, there are several esthetic disadvantages associated with breast restoration using prosthetic implants. These include visible rippling, capsular contracture, implant malposition, bottoming out, and implant exposure. A majority of these complications are due to tissue thinning from the expansion process, inadequate filling or incorrect placement of the implant, or over generous formation of the breast pocket.[2] Placement of an appropriately sized piece of acellular dermal matrix (ADM) between the implant and the skin can augment the skin thickness and act as a sling to support the implant, reducing the risk of complications (Figure 1).

Since ADM was first used in breast reconstruction in 2005,[3] a plethora of ADMs have become available on the market. However, the choice of which ADM to use can seem distressingly random. Most ADMs are derived from cadaveric tissues that are decellularized and often terminally sterilized using different proprietary techniques that are then performed to different degrees of intensity.[16] This results in different storage requirements, shelf lives, intraoperative preparation methods, and costs. Furthermore, pharmaceutical companies may stress these differences in sterility to show that their products are safer than those of their competitors.

Currently, surgical practice is based more on product availability or anecdotal experience than on scientific data. While more recent studies have begun to objectively study the difference in outcomes between ADM products,[4–9] randomized prospective studies with supporting histologic

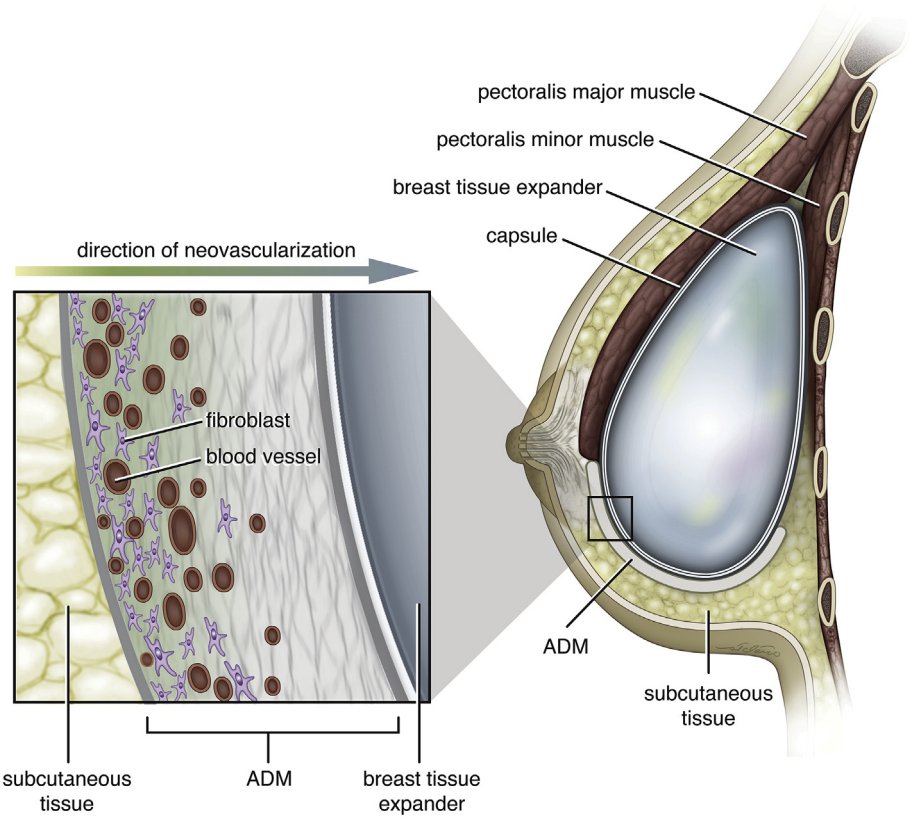

Figure 1 The illustration shows the placement of ADM between the skin and the breast implant to provide an additional layer covering the implant. The integration of the ADM to the recipient tissue occurs with fibroblast and vessel ingrowth.

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data are lacking. In this study, we compared two ADM products in use at University of California Davis, Alloderm Ready To Use (RTU)® (LifeCell Corp., Branchburg, NJ) and Allomax™ (Bard Davol Inc., Cranston, RI) (Table 1), in a single-blinded, prospective randomized controlled trial, focusing on clinical outcomes, patient satisfaction, and histologic differences.

Materials/methods

Study design and patient selection

The study was approved by the University of California Davis Institutional Review Board (protocol # 415153-2). For our power analysis, we set $\alpha = 0.05$ and β (power) $= 0.08$. The Jansen et al. review of Alloderm use in breast reconstruction showed an infection rate of 0–11%.[10] When excluding direct-to-implant reconstructions and papers with fewer than 11 total patients, the average infection rate in these studies was 3.38 ± 2.30. Less has been published on Allomax, a relatively newer product, but the literature has estimated the infection rate at 1%.[11] On the basis of this data, we determined that 15 patients would need to be enrolled in each study arm.

The criteria for enrollment included any patients over 18 years of age or older seeking a two-stage expander to implant-based breast reconstruction. Patients who were enrolled were then randomized in a 1:1 ratio to AlloMax or AlloDerm RTU arms using a blocked randomization scheme. Randomization was performed in two strata, one consisting of subjects who were nonsmokers and nondiabetic and the other consisting of smokers and/or diabetics.

Table 1 Product specifications for Alloderm RTU® and Allomax™.

	Alloderm RTU	Allomax
Decellularization process	Sodium chloride + Sodium deoxycholate + freeze drying	Tutoplast® process
Storage	Room temperature	Room temperature
Rehydration	2 min	5 min
Directionality	Basement membrane and dermal side	None[b]
Shelf life	2–5 years	5 years
Contraindications	Allergy to Polysorbate 20 or any of the antibiotics used in processing of the tissue as listed on the outer package	
SAL[a]	10^{-3}	10^{-6}

[a] SAL = Sterility Assurance Level: Only Allomax meets the Food and Drug Administration's standards for sterility, which requires a SAL of 10^{-6} or less.
[b] A newer product, marketed specifically for bilateral breast reconstruction, is sided.

In the first operation, a tissue expander and ADM were placed. Patients were examined at postoperative 7, 14, and 30 days for drain care and wound evaluation (Table 2). Drains were left in place until output was <20 mL/day on two consecutive days. Expansion started on average 30 days postoperatively (Table 2). Patients were monitored in clinic throughout the expansion process and for 1 year after implant placement (Table 2). Our primary clinical outcome measure was the complication rate, including the need for expander removal, skin necrosis, infection, seroma, hematoma, and skin necrosis. Patient satisfaction was evaluated 1 year after implant exchange using the BRECON-31 questionnaire, which is a validated breast reconstruction satisfaction questionnaire.[12,13]

Surgical technique

All procedures were performed by a single academic surgeon using a standardized operative technique. During the first stage of reconstruction, subpectoral pockets were created. The wounds were irrigated with a triple antibiotic solution containing 50,000 units Bacitracin (Pfizer, New York, NY), 1 g of Cefazolin (GlaxoSmithKline, Middlesex, UK), and 80 mg Gentamicin (Baxter, Mississauga, ON) in 1 L of normal saline. The chosen ADM was then prepared according to the manufacturer's instructions, cut to size, and secured to the inframammary fold. The tissue expanders (Mentor, Santa Barbara, CA) were then placed in the subpectoral pocket and inflated to fill the dead space. Two drains were placed, one in the subpectoral pocket and another in the subcutaneous pocket, and the skin flaps were closed over the pectoralis muscle in a standard fashion.

During the second stage of the reconstruction, the prior mastectomy scar was reopened and the expander was removed. Depending on the level of capsule formation, a capsulotomy or capsulectomy was performed. For the first 10 study patients, a 1×1 cm biopsy of the ADM was taken from the matrix edge and transferred to the laboratory for further histological analysis. After appropriate sizing, the implant was placed in the pocket using an atraumatic, no touch technique, and the wounds were closed in the standard fashion.

Table 2 Timetable for the procedures performed during the study.

Procedure	Postoperative day (POD)
ADM[a] and TE[b] placement	POD 0
Clinic follow-up visit	POD 7
Clinic follow-up visit	POD 14
Clinic follow-up visit & start of expansion	POD 30
Implant exchange and ADM biopsy[c]	variable
Clinic follow-up visit	POD 1 year

[a] ADM = acellular dermal matrix.
[b] TE = tissue expander.
[c] Definitive reconstruction was delayed at least 4 weeks after completion of chemotherapy and 12 months after radiotherapy.

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Histological analysis

The biopsy specimens were processed and embedded in paraffin blocks. The embedded samples were cut into 10 μm sections, and two slides per specimen were stained with hematoxylin-eosin (HE). Stained slides were examined under 20× magnification, and five pictures were taken from each of the dermal, middle, and implant portions of the ADM totaling 15 pictures per section (Figure 2). Blood vessels in each image were counted manually using ImageJ software (Rasband, W.S., ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, http://imagej.nih.gov/ij/, 1997–2016). With two sections per slide, we could obtain 20 different vessel/high power field (HPF) counts for each of the upper, middle, and lower rows in each ADM biopsy specimen.

To further assess vascular ingrowth, von Willebrand Factor (vWF) immunofluorescence (IF) staining was performed. In addition, fibroblast and macrophage infiltrations in the ADM biopsies were evaluated by anti-fibroblast and CD68 IF staining, respectively. Briefly, slides were incubated with the primary antibodies for vWF (Abcam, Ab6994, Cambridge, MA), fibroblast (EMD Millipore, CBL271, Billerica, MA), and CD68 (Santa Cruz Biotechnology Inc., sc-7082, Santa Cruz, CA) for 1 h at room temperature. The primary antibodies were tagged with Alexa Fluor 488 (AF488)-labeled anti-goat, anti-mouse, and anti-rabbit IgG (Invitrogen, Eugene, OR). The nuclei were counterstained with 4′,6-diamidino-2-phenylindole (DAPI) (Vector Laboratories, Burlingame, CA), and the images were captured under a fluorescence microscope. The areas with positive fluorescence were quantified using ImageJ software by selecting the stained areas with the threshold function and then quantifying these areas with the measure function.

Cost analysis

We collected information on supply charges from Bard Davol Inc. or LifeCell Corp. Hospital charges to insurance companies and insurance payouts were obtained from the University of California Davis Medical Center Billing Department. These payments were tracked using the CPT code 15777, which applies specifically for the placement of a biologic implant such as ADM.

Statistical analysis

Statistical analysis was performed using VassarStats: Webpage for Statistical Computation (http://vassarstats.net/). All comparisons were run using either the two-tailed t-test or one-way ANOVA for comparisons of multiple samples, or n−1 two proportion test for binary values. A p value < 0.05 was considered statistically significant.

Results

Clinical results

Patients were followed for a minimum of 1 year after implant exchange operation. The demographics of two study arms were roughly equivalent (Table 3). Operative demographics were also similar between the study arms ($p < 0.05$) (Table 4). Two patients in the Alloderm arm transferred care to another institution midway through

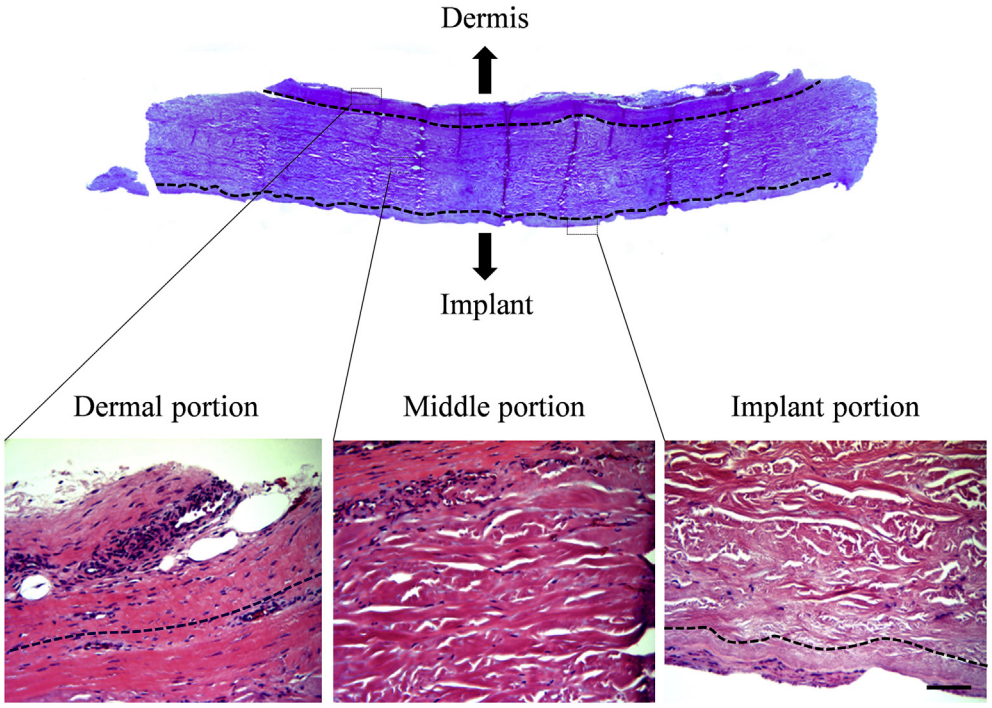

Figure 2 The HE-stained ADM sections were divided into three rows as dermal, middle, and implant. Pictures were taken from each row under the microscope. Microbar 100 μm.

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Table 3 Patient demographics.

	AlloDerm RTU, n (%)[a]	AlloMax, n (%)[a]
Age (range)	49 (25–63)	51 (31–63)
BMI	25.4 (20.3–33.1)	25.9 (21.5–30.8)
Pre-op RT	2 (13.3)	2 (13.3)
RT during expansion	3 (20)	2 (13.3)
Diabetes	2 (13.3)	1 (6.7)
Smoking	1 (6.7)	1 (6.7)
Total subjects	**15**	**15**

[a] n = patient number, RT = radiotherapy, BMI = body mass index.

Table 4 Operative demographics.

	AlloDerm RTU, n (%)[a]	AlloMax, n (%)[a]
Unilateral	5 (20)	7 (46.7)
Bilateral	10 (40)	8 (53.3)
Initial expander fill	123.08 ± 64.06 mL	106.08 ± 46.09 mL
Drain days		
Drain 1	6.8 ± 2.6	7.7 ± 3.9
Drain 2	17 ± 5.3	15.2 ± 3.4
Expansion time[b]	249 ± 137.5	243 ± 101.2
Total subjects	**15**	**15**

[a] n = patient number.
[b] The average expansion time for those undergoing postoperative chemotherapy or radiotherapy was 260 days.

expansion. Figure 3 shows representative patients from each group.

Major 30-day complications were defined as those requiring a return to the operating room. The rate of major complications in the Alloderm arm was 8.0% vs. 4.3% in the Allomax arm. Overall, there was no significant difference between the groups in terms of major 30-day complications ($p > 0.05$) (Table 5). The rate of minor complications on postoperative day 30 was 0% and 13.0% in Alloderm and Allomax arms, respectively ($p > 0.05$). For any 30-day complication, the rate was 8.0% vs 17.4% in the Alloderm vs. Allomax arms ($p > 0.05$) (Table 5).

There were no major complications in the Alloderm arm after implant exchange operation (Table 5). One patient in the Allomax arm had a grade IV capsular contracture, requiring capsulectomy, and another patient with a history of radiotherapy to the area had implant exposure requiring implant removal (Table 5). Of note, the grade IV contracture patient did have a history of intrinsic scarring but had refused flap reconstruction. She developed this contraction despite a complete capsulectomy at time of implant exchange and prophylactic Montelukast.

The difference between major complication rates after implant exchange (0% in Alloderm vs. 8.9% in Allomax arms) was not significant ($p > 0.05$). The rates of any major complication throughout the complete reconstructive course (8.0% in Alloderm vs. 13% in Allomax), expander loss (4.0% Alloderm vs. 8.7% Allomax), or other complications (8.0% Alloderm, vs. 26.1% in Allomax) were not statistically significant ($p > 0.05$).

One year after permanent implant placement, patients were asked to fill out the BRECON-31 satisfaction questionnaire. We had a 43.8% response rate to this questionnaire, with patient responses being similar across all metrics.

No statistically significant difference was observed between reimbursement for AllodermRTU and Allomax. The negotiated price of a 6 × 16 cm sheet of Allomax was 12.4% less than the negotiated price for Alloderm RTU at our institution. Both were billed under the CPT code 15777, and the amount billed to the insurance company was either $679.00 or $723.00, regardless of the type of ADM used. Average reimbursement for one sheet of AllodermRTU was $298.6 ± 203.6, vs. $211.2 ± 133.4 for a similarly sized piece of AlloMax ($p > 0.05$). Because of the diversity of insurance companies in our patient population, we could not draw a definitive conclusion whether ADMs were reimbursed differently by the same insurance company. However, the data that we have suggest that there is none.

Histologic results

The mean vessel number/HPF in the Allomax specimens was 6.50 ± 4.9 at the dermal portion, 2.84 ± 3.3 at the middle, and 1.36 ± 2.09 at the implant portion. The difference between these portions was statistically significant ($p < 0.01$) (Figure 4). Comparable values in the Alloderm arm were 5.37 ± 2.8, 1.76 ± 2.4, and 1.06 ± 1.8, respectively. The difference between the portions was again significant ($p < 0.01$) except for the middle vs. implant portion comparison, which trended toward but did not achieve significance ($p = 0.08$). On the basis of these findings, there was statistically significant evidence of vessel in-growth from the dermal surface of both ADMs.

When comparing Alloderm to Allomax, there were significantly more vessels in the middle portion of Allomax ($p < 0.05$) with a trend toward the significance at the dermal portion ($p = 0.08$). The difference between the vessel numbers in implant portions was not significant ($p > 0.05$) (Figure 4).

Both Alloderm and Allomax specimens had significantly more fibroblasts at the dermal portion ($p < 0.01$). The proportion of positively stained areas in dermal, middle, and implant portions was 4.37 ± 3.9%, 1.15 ± 1.5%, and 1.63 ± 1.5% of the whole surface area of HPF (% HPF) in the Allomax arm and 3.51 ± 2.9%, 0.91 ± 1.2%, and 0.91 ± 1.03% HPF in the Alloderm arm. While the Allomax arm had consistently higher amount of fibroblasts than the Alloderm arm, none of these differences achieved significance ($p < 0.05$) (Figure 5).

The proportion of CD68-stained areas also decreased from dermal toward the implant side of the ADM in both the Alloderm and Allomax specimens, although the difference between the portions did not achieve significance ($p > 0.05$). CD68-positive areas were 3.81 ± 3.6%, 3.03 ± 3.5%, and 2.24 ± 2.2% HPF for the dermal, middle, and implant side in the Alloderm arm and 3.79 ± 2.3%,

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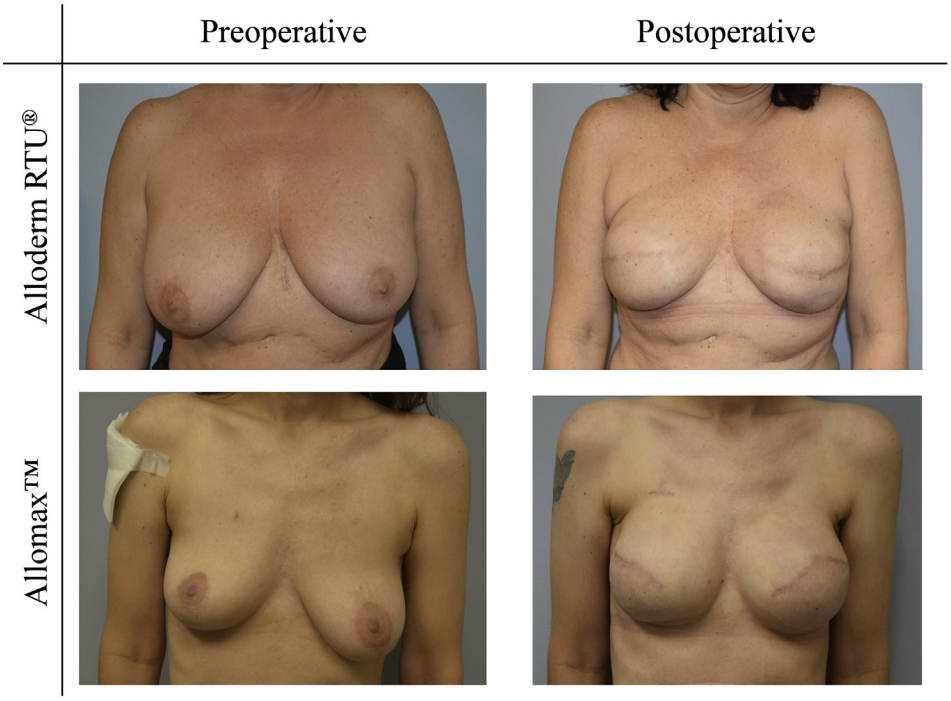

Figure 3 The figure shows preoperative and postoperative pictures of representative patients from Alloderm and Allomax groups.

3.24 ± 2.02%, and 2.56 ± 1.8% HPF for the Allomax arm, respectively. No significant difference was observed between the two study arms (Figure 6).

Discussion

Several papers have been published in the last 5 years comparing different ADMs from a histologic or a clinical outcomes perspective, many sponsored by industry. Studies focusing on histology tried to determine the clinical implications using only the histological data while clinical investigations did not study the underlying histology. Our study seeks to address this gap in the literature by simultaneously addressing both issues in detail with a prospective, randomized study.

Histologic studies of ADM implantation in rat and porcine models have consistently shown vascular ingrowth and inflammatory cell penetration into the ADM, in both sterile and aseptic matrices.[8,14,15] However, these studies have not been consistent with regard to which ADM is associated with greater cellular and vascular ingrowth. In our study, we found statistically significant evidence of vessel ingrowth from the dermal side of the matrix and found evidence of greater ingrowth into the Allomax product, with more vessels present per HPF in the middle of the ADM than the same site in the Alloderm product. In addition, we found evidence of fibroblast infiltration from the dermal side of the matrix in both ADMs, but no significant difference was found between products. One potential reason that these products acted more similarly in our study than in previous animal studies[14] could be because we used Alloderm RTU, which is now sterilized, unlike the earlier Alloderm RTM product. The demographic differences between study arms in our study (e.g., diabetes, radiotherapy, smoking, and obesity) might also have acted as a confounding factor to account for the differences in incorporation on a histological level. However, the prospective randomized nature of our study should have minimized such confounding.

Fundamentally, the question that surgeons want to answer is whether the differences in processing between ADM products lead to any difference in clinical outcomes. Alloderm has been on the market for a long time, and as

Table 5 Clinical complications.

Postoperative 30 day		
	Alloderm RTU, n (%)[a]	Allomax, n (%)[a]
Major		
TE[b] exposure	1 (4)	1 (4.3)
Hematoma	1 (4)	
Minor		
Wound necrosis	—	1 (4.3)
Seroma	—	1 (4.3)
Cellulitis	—	1 (4.3)
Postexchange		
Major		
Implant exposure,	—	1 (4.3)
Grade IV contracture	—	1 (4.3)
Minor	—	—
Total	**2 (8)**	**6 (26.1)**

[a] n = number of breasts.
[b] TE = tissue expander.

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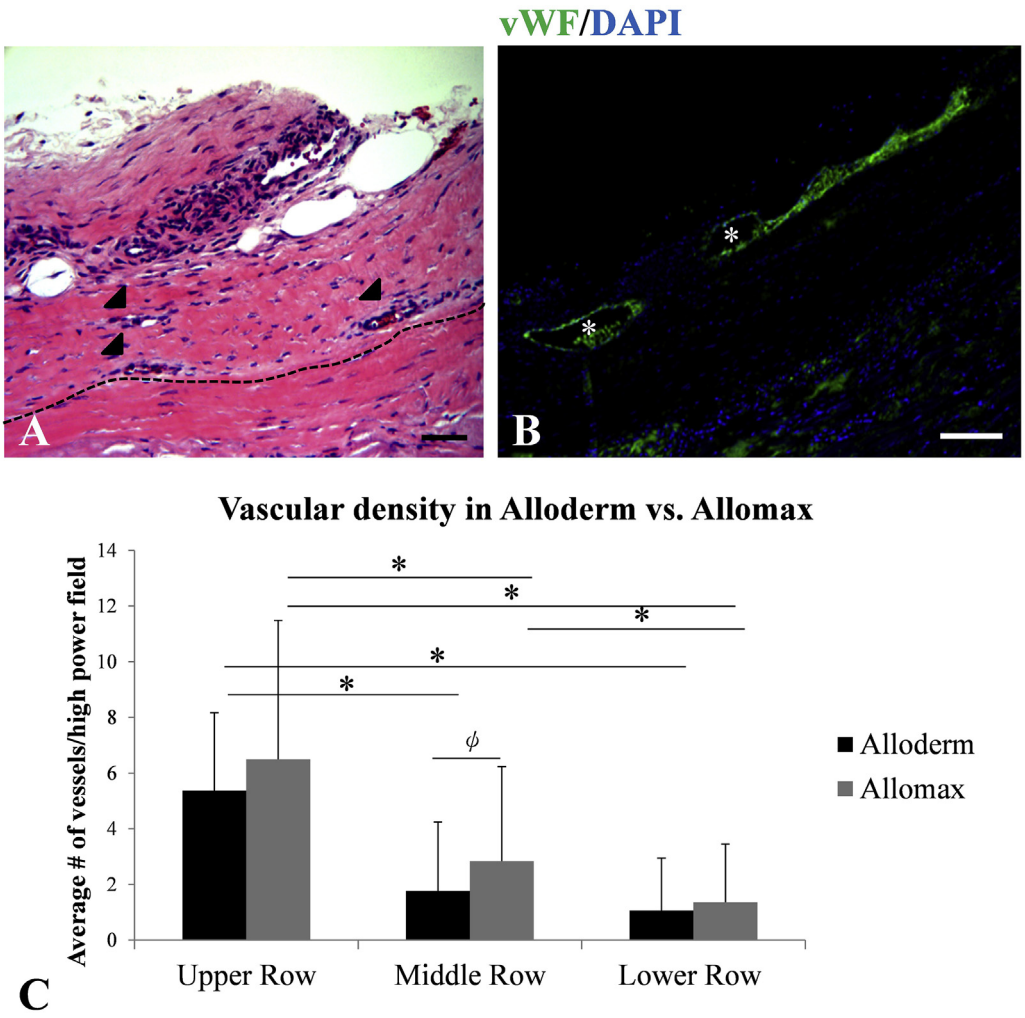

Figure 4 (A) Vascular density (average number of vessels/high power field) calculation in each row of ADMs was performed depending on HE staining. Black arrowheads indicate the vessels. Microbar 100 μm. (B) The presence of vessels was also confirmed with vWF IF staining. White asterisks (*) are in the vessel lumens. Microbar 200 μm. (C) The graph shows the comparison of vascular density of the rows between the groups. *$p < 0.01$, $^{\psi}p < 0.05$.

such, this is the product that other products are most frequently compared against. Retrospective studies comparing Alloderm to Surgimend®,[4] Strattice™,[7] FlexHD®,[17] and DermaMatrix™[9] have failed to show a significant difference between the clinical outcomes of these ADM products. However, it is important to note that the Alloderm product studied in these reviews is the earlier RTM product. Studies comparing Alloderm RTM to the terminally sterilized RTU product have shown the risk of infection with Alloderm RTU use is lower,[18] but the risk of seroma formation is significantly higher,[19] differences that may be attributable to the changes in preparation and sterilization. The only other prospective trial to date, comparing Alloderm vs. Dermamatrix, found no significant difference in complication rates between the two products but did see a significantly shorter number of expansion days in the Alloderm group vs. the DermaMatrix group (70 vs. 42 days, $p < 0.001$).[6] The authors attributed this difference to anecdotal experience that Alloderm is more pliable; however, no histological or objective pliability data accompanied this conclusion.

Our 30-day complication rates of 4.3% and 8% for major complications and 26.1% and 8% for any complication rate are consistent with the published data and compare favorably to other randomized controlled trials.[6] Also in keeping with the literature, our rate of comorbidities such as smoking, diabetes, or prior radiotherapy were seen at a higher rate in patients who had complications across both arms (37.5% of patients who developed a complication had a comorbidity vs. 20.1% in the study population).

Our drain data were also similar to the published rates and were not significantly different between study arms. One notable data point in our study was that our expansion time was much longer than that in other studies, even accounting for the difference between patients requiring postoperative chemotherapy or radiotherapy. Postulated reasons for this include low intraoperative expander fill (just over 100 mL on average for both arms) and that patients were given the option to expand more slowly (every other week or less) to decrease the discomfort of expansion and the risk of flap necrosis.

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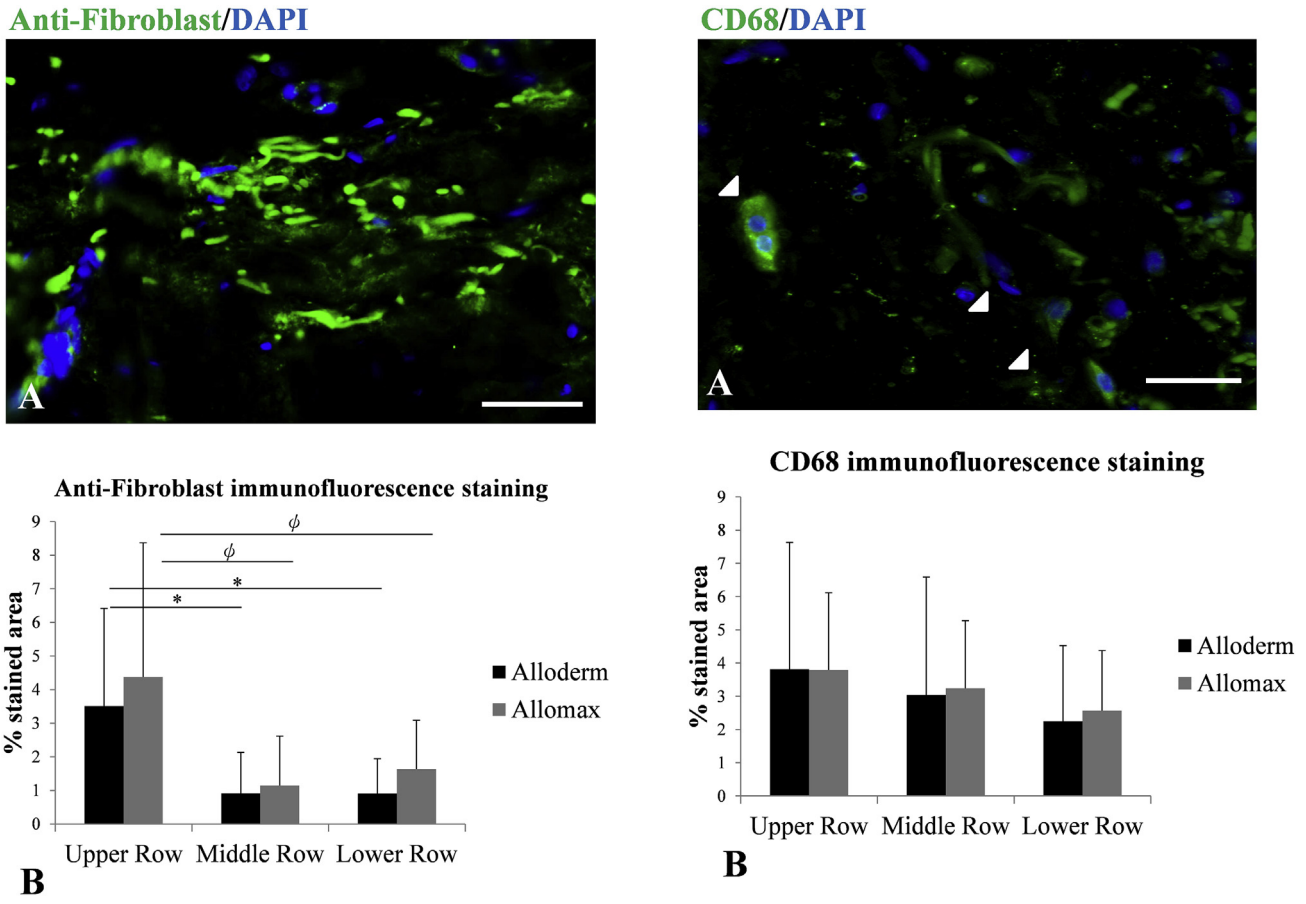

Figure 5 (A) Anti-fibroblast staining revealed the extent of tissue invasion into ADMs. Microbar 100 μm. (B) Fibroblast staining was similar between the study arms. Fibroblast infiltration was significantly higher in the upper rows in both ADMs in comparison to middle and lower rows. *$p < 0.01$, $^{\Psi}p < 0.05$.

Figure 6 (A) CD68 IF staining was performed to evaluate the extent of inflammatory reaction toward the ADMs. White arrowheads indicate the CD68-positive inflammatory cells. Microbar 100 μm. (B) CD68 staining was similar between the study arms ($p < 0.05$).

Lack of statistically significant clinical and histologic outcomes between the two ADMs suggests that cost could be used as a determining factor in deciding what ADM to use and surgeon preference with the different handling properties. While there has been an anecdotal discussion at our institution about lower reimbursement for non-Alloderm products, our data found that this was not the case. Because the University of California Health System uses the same billing code for both Alloderm and Allomax, no significant difference was observed in reimbursement between arms. In addition, we subdivided our cost data by an insurance carrier to determine if the same carrier reimbursed differently for Alloderm vs. Allomax. Because of the diversity of insurance carriers, we could make two such comparisons (Medicare and Blue Shield). Making this comparison, there did not appear to be a difference in reimbursement between ADM types.

Our study provides a high level of evidence but was limited by its power. While the previous literature suggested that a sample size of 15 patients per arm would be sufficient to see a clinical difference, we did not consider that the newer Alloderm RTU might behave similarly to Allomax, perhaps because of its increased sterility.

Conclusion

This study demonstrates an acceptable safety and outcome profile with both Alloderm RTU and Allomax use in immediate breast reconstruction. In this prospective randomized trial, differences in processing and sterilization did not equate to large differences in histologic and clinical outcomes, although there was greater vessel ingrowth seen into the Allomax product and a trend toward more minor complications in the AlloMax arm. In the absence of objective clinical differences, we believe that surgeon preference and cost should be considered when deciding which ADM to use for breast reconstruction.

Conflict of interest or funding

None.

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