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Breast

Cortiva Versus AlloDerm Ready-to-use in Prepectoral and Submuscular Breast Reconstruction: Prospective Randomized Clinical Trial Study Design and Early Findings

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Background: Several acellular dermal matrices (ADMs) can be used to provide soft-tissue support for post- and prepectoral prosthetic breast reconstructions. Yet, several recent meta-analysis suggest that due to a lack of rigorous evaluation in the setting of head-to-head prospective randomized control trials, few reliable conclusions regarding performance outcomes can be drawn. We compare Cortiva 1 mm to AlloDerm RTU in the setting of submuscular reconstruction in one study, and prepectoral in the second. Moreover, we present the findings from the interim analysis in our submuscular study.
Methods: Using a single-blinded prospective randomized control trial design, we compare outcomes in 180 patients undergoing submuscular breast reconstruction with 16×8 cm ADM support (either Cortiva 1 mm or AlloDerm RTU). A parallel study evaluates 16×20 cm sheets of these ADMs in 180 patients undergoing prepectoral reconstructions. Time to drain removal, complications, fill volumes, patient-reported outcomes, and narcotic consumption are prospectively evaluated.
Results: Interim analysis of 59 breasts in the submuscular study arm (Cortiva n = 31; AlloDerm n = 28) revealed no statistically significant differences with respect to outcome. At the time of interim analysis, the AlloDerm RTU group contained a higher proportion of never-smokers ($P = 0.009$), while patients implanted with Cortiva 1 mm received a larger tissue expander ($P = 0.02$).
Conclusion: We present a protocol for a robust randomized control trial to evaluate outcomes in both submuscular and prepectoral prosthetic breast reconstruction assisted by 2 distinct types of ADM. Our interim analysis reveals no evidence of inferiority of outcomes in a comparison of AlloDerm to Cortiva. *(Plast Reconstr Surg Glob Open 2018;6:e2013; doi: 10.1097/GOX.0000000000002013; Published online 13 November 2018.)*

INTRODUCTION

Acellular dermal matrices (ADMs) are broadly utilized as an adjunct to prosthetic breast reconstruction. They offer soft-tissue support to maintain the lateral and inframammary folds and can facilitate a match of the dimensions of the periprosthetic lamella with the mastectomy skin flap envelope.[1,2] ADMs are distinguished from one another by their clinical performance, traditionally measured by complication rates, and by their cost, a factor that will become even more critical with bundled payment models on the horizon.[3–7] The cost of using an ADM not only includes its price and impact on expensive reconstructive failures but also its potential for limiting the number of downstream reconstructive interventions.[3,4,8,9] Increased

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initial cost of one product over another may be justifiable if it increases overall value-based care by improving outcomes and/or limiting future procedures.[9]

Although a large body of evidence exists evaluating the safety and complication rates associated with ADM-assisted prosthetic breast reconstruction, there is a surprising dearth of high quality (level 1 or level 2 evidence) studies, including prospective randomized controlled trials (RCTs), on the topic. This is a significant limitation that diminishes the utility of recent meta-analyses on ADM use in prosthetic breast reconstruction and prevents clinicians from effectively interpreting the results of these studies without the presence of bias inherent in retrospective study designs.[10–12] The BREAST trial, the first RCT to compare ADMs in submuscular breast reconstruction, showed that overall complication and implant loss rates with freeze-dried AlloDerm were comparable with DermaMatrix using a noninferiority design.[13–15] A subsequent RCT comparing ADM slings in submuscular reconstructions failed to demonstrate significant differences in outcomes between AlloDerm RTU and AlloMax. This study, however, may have been underpowered as complications rates of 8% versus 26.1% were not found to be significantly different.[16] To our knowledge, there are no published RCTs comparing ADMs to one another when used in prepectoral breast reconstruction, an increasingly popular technique for prosthetic reconstruction Given the lack of high-quality studies available, a significant need remains for carefully designed and adequately powered RCTs comparing outcomes between various ADMs in submuscular and prepectoral prosthetic breast reconstruction.

Cortiva is a Tutoplast-sterilized human ADM with similar vascular, collagen, and elastin remodeling characteristics when compared with AlloDerm on histological analyses.[17] To date, there are limited studies comparing complication rates and outcomes between Cortiva ADM and AlloDerm ADM. The only existing studies have demonstrated similar complication rates; however, these are limited by their retrospective study design.[18–21] In this study, we introduce a robust RCT study design to compare clinical and patient-reported outcomes between Cortiva ADM and AlloDerm RTU ADM when used as a sling to support tissue expanders placed in the submuscular location in one study arm, and prepectoral reconstructions with tissue expanders (TEs) or direct-to-implants (DTI) in a separate study arm. Furthermore, we present results from our interim analysis of the submuscular study arm.

METHODS

Study Design

We are conducting a prospective, single-blinded, randomized control trial comparing AlloDerm RTU (Allergan Medical, Irvine, Calif.) medium thickness (1.6±0.4 mm) to Cortiva 1 mm (RTI Surgical, Alachua, Fla.) Allograft Dermis (1.0±0.2 mm) in the practices of TMM and MMT. Patients undergoing submuscular breast reconstruction with a TE and 16×8 cm ADM sling consisting of either AlloDerm or Cortiva are compared in one study arm. Patients undergoing prepectoral breast reconstruction with either DTI or TE supported by a 20×16 cm ADM sheet are compared in a separate study arm. In both arms, randomized patients are allocated 1:1 to one ADM or the other. This study is approved by our institutional review board (201606168) and listed on clinicaltrials.gov (NCT02891759).

We began enrolling patients for submuscular reconstruction using an ADM sling in February 2017. We subsequently noted a significant shift to prepectoral reconstructions both nationally and in our own practices,[22,23] and added the prepectoral arm to optimize enrollment rates and reflect our own pattern of practice. We determined that the perceived and reported differences between prepectoral and submuscular reconstructions like pain and animation deformity would be too profound,[24,25] and create too much variability to be included in the same analysis and so parallel prepectoral and submuscular arms were initiated (Fig. 1).

Patient Selection

Female patients, aged 22–70 years old, undergoing immediate prosthetic reconstruction following therapeutic or prophylactic skin- or nipple-sparing mastectomy with a body mass index (BMI) less than 36 kg/m^2 are enrolled. We have excluded patients who are pregnant, breastfeeding immediately before mastectomy, unwilling to sign or unable to comprehend written informed consent. The decision to proceed with prepectoral or submuscular reconstruction with either a TE or DTI is determined preoperatively. Our consent process, however, maintains flexibility to choose the alternative plane for implant placement, and device type, if determined clinically appropriate by the plastic surgeon. In those instances, we would continue to use the ADM to which the patient was randomized (ie, if the patient was told they would most likely receive a prepectoral immediate implant and was randomized to a 20×16 cm AlloDerm RTU preoperatively, but was intraoperatively switched to a submuscular TE, then the patient would be switched to the submuscular study arm and would still receive AlloDerm RTU, but a 16×8 cm sheet instead).

Surgical Procedure for Submuscular Reconstruction with Acellular Dermal Matrix Sling

Submuscular reconstructions are performed immediately following a skin- or nipple-sparing mastectomy. The pectoralis major muscle is elevated by releasing its caudal attachments to create a submuscular pocket that accommodates a TE selected based on base width, mastectomy specimen weight, and patient goals. Using absorbable suture, through transverse incisions, the ADM is secured along the medial, lateral, and inframammary fold, the TE placed, and the caudal edge of the pectoralis sutured to the cephalad leading edge of the ADM. For lateral radial incisions, the ADM is secured medially and centrally, the TE placed, and ADM inset completed along the lateral mammary fold. For inframammary incisions, the ADM is secured to the caudal edge of the pectoralis and the medial and lateral mammary folds defined be-

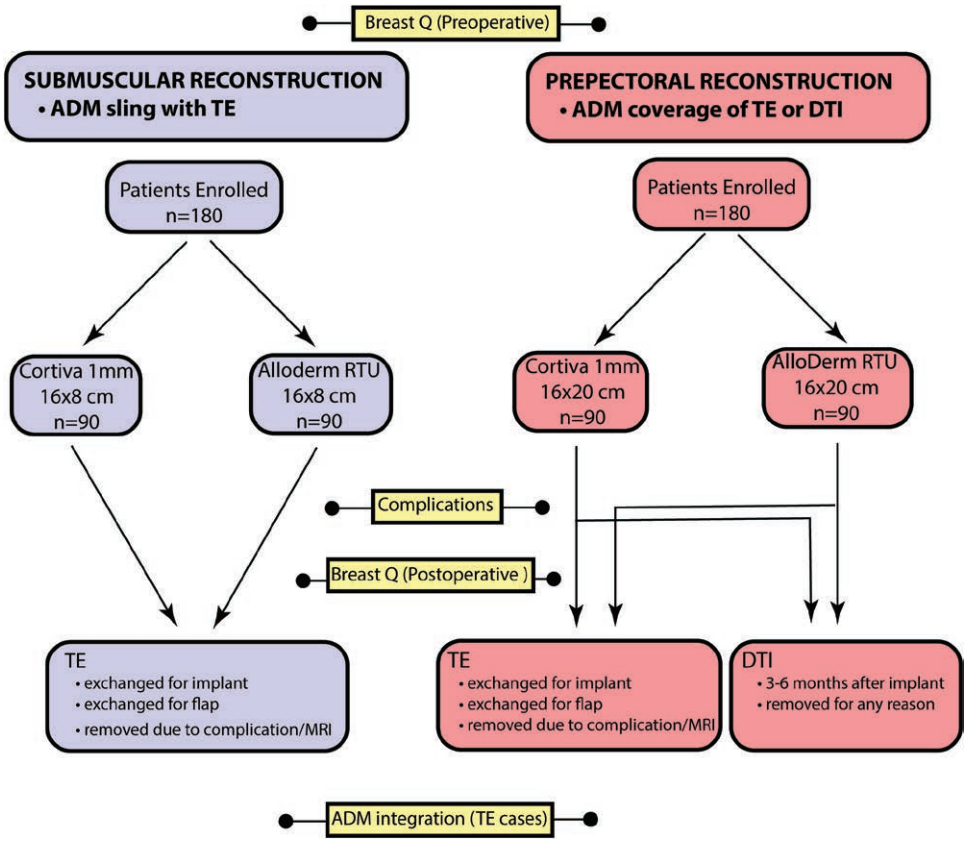

Fig. 1. Flowchart for randomized clinical trial study design including study arm, enrollment numbers, and outcome metrics.

fore the TE is placed and the ADM secured to define the inframammary fold.

Surgical Procedure for Prepectoral Reconstructions with Acellular Dermal Matrix

The ADM is manually fenestrated and tacked superiorly to define the upper pole of the reconstruction after which the medial and lateral mammary folds are defined by the ADM with absorbable, tacking sutures. DTIs are placed if the skin envelopes are deemed adequately perfused by clinical judgment occasionally supplemented with indocyanine green and laser-assisted imaging. In these cases, the ADM is draped over the implant with sufficient tension to minimize the risk of malrotation. Otherwise, a TE is placed, tabbed to avoid malposition, with additional lower pole laxity accounted for with the inset. The inframammary border of the ADM inset is placed last, with a gutter to reinforce the integrity of the lower pole when sufficient ADM is available.

Study Endpoints

Patients undergoing TE placement in either study arm are followed until exchange with an implant, flap, or both, or premature device removal for any reason. Patients undergoing DTI reconstruction are followed for at least 3 months postoperatively. Patients undergoing reoperation of the surgical site without device exchange or removal are kept in the study. Breast-level data are independently collected for bilateral cases so if one device is removed or exchanged prematurely, the patient remains in the study until the contralateral breast is removed or exchanged for TEs, or at least 3 months postoperatively for DTIs. Date of drain removal, which occurs once output drops below 30 cc for 24 hours, is prospectively recorded.

Outcome Measures

The primary outcome measure, analyzed at the breast-level, is premature explantation of the TE before exchange, or unintended explantation of a DTI reconstruction before 3 months. Secondary breast-level outcome measures include other complications like seroma, cellulitis, wound or ADM dehiscence, or skin flap necrosis. We record TE or DTI device size, absolute and relative and final TE fill volumes, time to drain removal, reason for premature explantation, and the type and timing of final reconstruction upon TE exchange. At the time of TE removal, the decision to proceed to an implant exchange versus a flap was based on surgeon and patient preference with a bias toward flaps in radiated patients. ADM integration is semiquantitatively assessed at the time of TE exchange or TE or DTI premature removal using a grading scale outlined in Table 5 categorized as 0%, <50%, 50–99%, and 100% ADM integration. Patient level data include antibiotic use and narcotic consumption postoperatively. Patient-reported outcomes are measured with the pre- and postoperative Breast-Q

for all patients, and Qscore reported as an absolute value and ΔQscore for domains where pre- and postoperative values are generated.

Sample Size

Sample size determination was based on the primary hypothesis test for the incidence of premature TE or DTI removal. We assumed a premature TE or DTI removal rate of 20% as observed in one ADM group and 9% in the other ADM group in patients undergoing prepectoral reconstruction and in patients undergoing submuscular reconstruction, respectively. The hypothesized rates are based on published data from our group in >3,000 breasts who have undergone similar procedures.[7,26–28] For this phase 2 randomized control trial, we require 180 eligible patients, per arm, to achieve 80% power based on the 1-sided Z test with pooled variance to detect a difference between the incidence rates of the 2 ADMs at a 0.1 significance level.[29] We will separately compare the 2 ADMs among 180 patients receiving prepectoral and among 180 patients receiving submuscular reconstruction (Fig. 1).

Statistical Analysis

For the final analysis, we will use logistic regression models to assess the effect of ADM type accounting for other confounding factors like obesity, age, radiation therapy, chemotherapy, lymph node surgery, surgery type, and cancer stage on the presence of complications. Variables that are significant ($P \leq 0.2$) in univariate analysis and/or clinically relevant will be included in the multivariate logistic regression model.

Statistical analysis of Breast-Q data will be performed on 18 scales, derived from 6 modules of the Breast-Q for breast reconstruction.[21] The Breast-Q is scored on a 0–100 points scale (0-dissatisfied, 100-maximally satisfied) using QScore, which has been developed according to the Rasch model.[30] The Mann-Whitney *U* test will be used to detect the difference in data generated from evaluation of the Breast-Q, TE fills, drain use, and narcotic use between ADM types. The Gamma regression in the generalized linear model framework will be applied to model QScore with incorporation of other confounding factors.

Chi-square and the Fisher's exact test were used in the interim analysis to detect the association between ADM type and TE or DTI removal incidence and between ADM type and complications. For the interim analysis, we use descriptive statistics to describe the central tendency and variation of 3 outcome variables—physical well-being, satisfaction with information, and satisfaction with plastic surgeon in each arm. Then, we used a 2-sample *t* test to compare the mean of each outcome between the 2 ADMs. We also used the nonparametric Wilcoxon rank-sum statistic to compare the median of each outcome between the 2 ADMs. Statistical analyses were performed in SAS (Version 9.4, SAS Institute, Cary, N.C.) while descriptive statistics were analyzed and graphed in Prism (Version 7.0 for MAC, GraphPad Software, La Jolla, Calif.).

RESULTS

Patient Demographics and Surgical Details

Thirty-four patients (Table 1), whose 59 breasts were reconstructed with AlloDerm RTU (n = 17 patients, n = 28 breasts) or Cortiva 1 mm (n = 17 patients, n = 31 breasts) submuscular TE, completed the interim analysis (Table 2). Nearly half of the reconstructions were for prophylactic mastectomy, and there with no statistically significant differences with respect to BMI, race, incidence of radiation therapy, nipple-sparing mastectomy, bilateral cases, or chemotherapy. The AlloDerm RTU group (Table 2) was comprised of a significantly higher proportion of patients who had never smoked ($P = 0.009$). Mastectomy specimen weight, initial TE fill volume, percentage of the TE initially filled, and final TE fill volume was not significantly different between groups. The initial size of the TE selected was significantly larger in patients reconstructed with Cortiva 1 mm ($P = 0.02$).

Drain Removal

In most cases, the 10 French subpectoral drain was removed after the 15 French prepectoral drain, with removal of the final drain, regardless of size or location, occurring in 17.7 ± 7.0 days for AlloDerm RTU and 17.0 ± 7.6 days for Cortiva 1 mm. No significant differences were detected between cohorts (Table 3).

Table 1. Breast-level Descriptive Statistics of Patients Enrolled in the Submuscular Tissue Expander with ADM Sling Cohort

Variable	AlloDerm RTU	Cortiva 1 mm	*P*
N (breasts)	28	31	
Stage (%)	Prophylactic - 46.4	Prophylactic - 48.4	
	DCIS - 10.7	DCIS - 12.9	
	IA – 25.0	IA - 19.4	
	IB - 3.6	IIA - 12.9	
	IIA - 14.3	IIB - 3.2	
	IIB - 14.3	IIIA - 3.2	
Radiation (%)	0.0	3.2	0.62
Type of mastectomy (%)	60.7	41.9	0.15
Nipple-sparing	39.3	58.1	
Skin-sparing			

DCIS, ductal carcinoma in situ.

Table 2. Patient-level Descriptive Statistics of Patients Enrolled in the Submuscular Tissue Expander with ADM Sling Cohort

Variable	AlloDerm RTU	Cortiva 1 mm	*P*
N (patients)	17	17	1.0
Breast cancer diagnosis (%)	82.3	94.1	0.30
Age (y)	51.9 ± 12.1	47.5 ± 10.9	0.27
Race			0.32
White (%)	94.4	100	
Black (%)	5.6	0.0	
BMI (kg/m^2)	26.4 ± 5.2	26.8 ± 3.1	0.76
Smoking status			
Current smoker	5.8	17.6	0.30
Never smoker	88.2	47.1	0.009
Bilateral cases (%)	64.7	82.3	0.26
Chemotherapy (%)	23.5	35.3	0.23

Table 3. Summary of Procedure-related Data Reported at Breast Level

Variable	AlloDerm RTU	Cortiva 1 mm	*P*
N (breasts)	28	31	
Mastectomy specimen weight (g)	676.1±383.6	657.5±237.4	0.15
Tissue expander volume (mL)	496.4±117.0	554.8±76.7	0.02
Initial fill volume (mL)	164.6±125.0	191.3±95.4	0.52
Percentage of tissue expander volume initially filled (%)	32.2	35.6	0.39
Final fill volume (mL)	481.6±186.9	510.0±153.4	0.52
Time to 10 Fr subpectoral drain removal (d)	17.5±7.5	14.7±7.7	0.19
Time to 15 Fr prepectoral drain removal (d)	9.8±4.4	11.5±6.1	0.22
Time to final drain removal	17.7±7.0	17.0±7.6	0.57

Table 4. Summary of Complications Reported at Breast Level*

Variable	AlloDerm RTU	Cortiva 1 mm	*P*
N (breasts)	28	31	
Seroma N (breasts) (%)	3 (10.7)	0 (0.0)	0.06
Explantation N (breasts) (%)	0 (0.0)	1 (3.2)	0.35

*There were no explantations due to excess pain or magnetic resonance imaging.

Complications

Complications are presented in Table 4. A clinically detectable seroma was identified in 10.7% (N = 3) of breasts reconstructed with AlloDerm RTU and 0% with Cortiva 1 mm. Premature explantation was performed in no (0.0%) breasts reconstructed with AlloDerm RTU and 1 breast (3.2%) reconstructed with Cortiva 1 mm. The breast associated with explantation was also the only one affected by postoperative cellulitis, initially treated with oral doxycycline followed by intravenous cefazolin before ultimate explantation.

Timing to Second-stage and ADM Integration

Patients underwent planned exchange of TEs for implants or flaps (Table 5) within 145.6±51.6 days in the AlloDerm RTU and 167.0±61.5 days in the Cortiva 1 mm cohorts (*P* = 0.27). The majority of patients were exchanged with a breast implant alone, but 14.3% in the AlloDerm RTU and 26.6% in the Cortiva 1 mm groups (*P* = 0.25) received an autologous flap (Table 5). Integration of the ADM to the mastectomy flap (Table 5), determined by our semiquantitative analysis, was robust in the majority of patients with no significant difference between groups (*P* = 0.69).

Narcotic Use and Patient-reported Outcomes

Most patients stopped using narcotics for pain control within 1 or 2 weeks of the mastectomy with immediate reconstruction (Fig. 2). There were no significant differences between the AlloDerm RTU and Cortiva 1 mm cohorts with respect to physical well-being, or satisfaction with information or plastic surgeon (Table 6).

Table 5. Summary of Second Operation Details

Variable	AlloDerm RTU	Cortiva 1 mm	*P*
N (breasts)	28	31	
Time to second surgery (days)	145.6±51.6	167.0±61.5	0.27
TE exchanged with implant (%)	85.7	73.3	0.25
TE exchanged with flap (%)	14.3	21.4	
TE exchanged with flap + implant (%)	0.0	5.2	
Degree of ADM integration*	2.9±0.5	2.8±0.7	0.69

*"0" = 0% integration; "1" = <50% integration; "2" = 51–99% integration; "3" = 100% integration."

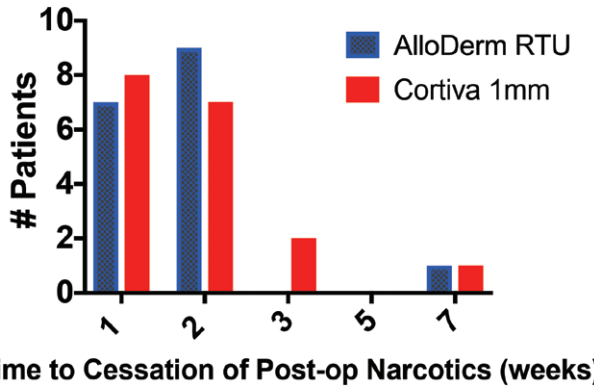

Fig. 2. Time to cessation of postoperative narcotics in submuscular TEs breast reconstructions with an AlloDerm RTU or Cortiva 1 mm sling.

DISCUSSION

Prosthetic breast reconstruction has benefited from the use of ADMs to provide soft-tissue support, maintain device position, and limit the manipulation of autologous tissues. Although abundant data support the use of ADMs,[31–37] several recent meta-analyses confirm the need for additional level 1 and 2 evidence to establish how one ADM compares to another and how they are influenced by patient and therapeutic factors. There are a limited number of randomized control trials specifically comparing one ADM to another when providing support for submuscular reconstructions,[13,14,16] and none, in the context of prepectoral reconstructions.

The original iteration of this trial excluded prepectoral breast reconstructions to minimize technique- versus ADM-associated variability. As our study progressed, how-

Table 6. Postoperative Patient-reported Outcomes Reported as Q-Scores

Variable	AlloDerm RTU	Cortiva 1mm	*P*
Physical well-being	30.4±12.0	30.5±13.4	0.69
Satisfaction with information	53.1±9.0	49.3±10.0	0.35
Satisfaction with plastic surgeon	46.1±4.9	42.8±7.9	0.22

ever, we noted a growing percentage of reconstructive breast implants in our practice, and nationally, were being placed prepectoral. Early data on prepectoral reconstructions suggest that they are associated with less pain,[25] less impact on range of motion,[38] higher initial and subsequent rates of TE fill volumes,[25] improved aesthetic outcomes,[23] less capsular contracture following radiotherapy,[39,40] and comparable complication rates to submuscular reconstruction.[39] That said, the prospective studies with long-term follow-up required to further delineate the advantages and indications for prepectoral breast reconstructions are lacking.[25,41–43] Therefore, expanding our study to specifically evaluate the performance of Cortiva versus AlloDerm RTU in prepectoral reconstruction has considerable value. Successful and sustainable prepectoral reconstruction may be even more reliant on the performance of one ADM over another. In addition to providing lateral and inframammary fold support, ADMs used for prepectoral reconstruction are relied upon to provide upper pole coverage, and are typically 2 to 2.5 times larger (increasing surface area that needs to incorporate) and more expensive.[22,23,39] Recognizing the benefit of studying prepectoral reconstructions, but acknowledging the marked differences with submuscular reconstructions that would preclude inclusion into the same cohort, we have added a separate prepectoral study arm comparing AlloDerm RTU to Cortiva 1 mm.

We chose a prospective randomized control trial design to control for population bias, and the numerous covariates that impact the heterogeneous population of women seeking immediate prosthetic breast reconstruction. Nonetheless, randomized control trials may possess unidentified biases that characterize those patients willing to participate in them, and are subject to patients who are lost to follow-up. Further, a substantially higher powered study would make our findings more robust, and along with longer term follow-up would enable us to study the impact of these ADMs on capsular contracture rates. Interim analysis of the first 34 patients to complete the submuscular arm of our study identified no statistically significant findings clearly attributable to the ADM. Moreover, none of the postoperative patient-reported outcome metrics evaluated differed based on ADM (Table 6). Notably, the composition of our study population closely resembled that of another RCT, the BREASTrial,[13] with some important exceptions. The BREASTtrial is skewed to a higher proportion of patients with stage III or greater cancers, radiation, and chemotherapy than our study (Tables 2 and 3). Our study, however, is comprised of a high percentage of smokers (Table 2), which reflects the general population.[44] Compared with the BREASTrial, patients in our study had drains for a shorter period of time (~17 versus 21 days), with fewer explantations (0–3.3% versus 5 to 11.2%). Preliminary data from our RCT also compares favorably to retrospective data obtained from Keifer et al.[18] that compares freeze-dried AlloDerm to Cortiva, albeit in a more heterogeneous population that included both TE and DTI reconstructions. The similar clinical performance metrics that we have identified between AlloDerm RTU and Cortiva may relate, in part, to similar-appearing ADM remodeling on gross examination. We found, using a semiquantitative assessment, no obvious differences in the degree of ADM integration at the time of TE exchange (Table 5). Upon histologic examination, Moyer et al.[17] have also noted similar levels of elastin deposition and revascularization of AlloDerm and Cortiva following prosthetic breast reconstruction.

CONCLUSIONS

High-quality evidence is needed to compare the performance of various ADMs used in prosthetic breast reconstruction. Prepectoral reconstructions represent a unique population within prosthetic breast reconstruction and have several notable differences when compared with submuscular reconstructions. As such, trials comparing ADM performance should separate these patient cohorts to eliminate the potential bias that plane of prosthesis placement can have on outcome. In this study, we outline a protocol for a robust RCT to evaluate complications, clinical outcomes, and patient-reported outcomes in both submuscular and prepectoral prosthetic breast reconstruction assisted by 2 distinct types of ADM. Interim analysis of a limited sample of submuscular reconstructions reveals no evidence of inferiority of outcomes in a comparison of AlloDerm RTU to Cortiva.

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