SyntheMed, Inc. REPEL-CV
Bioresorbable Adhesion Barrier Film

NATURE OF THE CLINICAL PROBLEM

Although under some circumstances it may be desirable to close the pericardium after a cardiac operation, conduits, grafts, and even compromised hemodynamics may preclude doing so. A scaffold of fibrin remains on the anterior surface of the heart on which humoral and cellular processes generate adhesions between it and surrounding tissues. In particular, retrosternal adhesions of varying density form when the operation has been performed through a sternotomy, the typical surgical approach.

If it is necessary to reoperate, these adhesions and scar formation increase complexity of every part of the operation; increase operative time; increase risk of intraoperative adverse events at resternotomy, during dissection, during cannulation for systemic perfusion and myocardial protection, and even during the heart operation itself; and increase intraoperative bleeding, leading to increased use of blood products.[1] Thus, for more than a quarter century, various innovations have been tested to make cardiac reoperation easier and safer.

APPROACHES TO THE PROBLEM

Perhaps simplistically we might say there have been four approaches to solve this clinical problem: 1) a permanent sheet of various materials placed between heart and sternum, 2) use of irrigating solutions intended to retard fibrin formation and thus adhesions, 3) bioresorbable membranes, and 4) scaffolds for autologous neopericardium regeneration. Walther and colleagues and Tsukihara and colleagues recently reviewed

progress in developing techniques in all these areas for facilitating sternal reentry, and they are well referenced by SyntheMed.[2,3] Briefly, in the 1970s and 1980s, permanent sheets of silicone rubber, PTFE and other polymers, as well as xenograft pericardium, were introduced for this purpose. By far the most commonly used product in the past and at present is a PTFE sheet sewn into place. However, use of permanent sheets and xenografts takes a little fussing and extra operative time, and they have not been widely adopted by the cardiac surgical community. They are perhaps more widely used in neonates, infants, and young children who undergo staged reconstruction of those congenital heart lesions that require one or more reoperations.

In the 1990s, various topical solutions were introduced. Some of these were pharmaceuticals directed at reducing the fibrin scaffold and reducing the inflammatory response.

Bioresorbable membranes were also introduced, either as a sprayable film or as an absorbable membrane with various rates of resorption. This is the category into which REPEL-CV fits.

To complete the picture, ongoing experiments and clinical trials that began in the 1990s introduce a scaffold or matrix on which an autologous neopericardium might form. This technology attempts simultaneously to reduce early adhesion formation and to regenerate a pericardium.

PROBLEMS WITH THESE APPROACHES

There have been a number of well-documented problems with all these approaches. In enumerating these, I hope to form the basis for a lively discussion of what outcomes should be considered in assessing safety of this technology.

1. Both permanent and temporary sheets are foreign bodies that can themselves incite an inflammatory response, leading at times to encapsulation, obliteration of dissection planes, and dense scar. Dr. Gosta Pettersson, a Scandinavian surgeon now at Cleveland Clinic, recalls a clinical trial in the 1990s in Sweden that was stopped prematurely when a bioabsorbable membrane being studied was found to incite a severe inflammatory response that resulted in rapid formation of a dense scar, making reentry extraordinarily difficult.[4-6] Needless to say, all the materials that are being used and tested today are ones that surgeons expect will not incite an even worse situation than does unaided healing.

2. Both permanent and temporary sheets may stimulate scar formation on the surface of the heart, which at reoperation obscures underlying cardiac architecture and structures such as coronary arteries. This was not assessed in REPEL-CV studies.

3. Permanent sheets do not grow, so when placed in babies, the possibility exists for them to distort surrounding growing structures. This, too, was not assessed.

4. Most permanent sheets are opaque, so when they are placed over the anterior surface of the heart, the heart is no longer visible during sternal closure. An advantage of many resorbable membranes such as REPEL-CV is that they are transparent.

5. Both permanent and bioresorbable sheets are sutured to surrounding tissue to prevent their migration. The necessary sutures are also foreign bodies, as noted by SyntheMed.

6. Not all materials are long-term biocompatible, and they require the extensive material testing that REPEL-CV has had to endure. However, the data before us cannot be considered long term.
7. Above all, the presence of a foreign body, either permanently or temporarily, is a nidus for mediastinal infection. Perhaps more than anything else, this has prevented widespread adoption of these products, particularly given the relatively infrequent need for reoperation.

REPEL-CV

With that background, we examine the efficacy (that is, benefit) and safety (that is, risk) of REPEL-CV, a bioabsorbable membrane intended to reduce occurrence (I prefer that word to “incidence,” which implies “per unit time”), severity, and extent of substernal adhesions in patients undergoing cardiac surgery via sternotomy. Four human trials have been conducted: 1) a short-term small, randomized, essentially single-center pilot trial in adults; 2) a small randomized pilot trial in neonates requiring staged operation and having planned delayed sternal closure so that both very early prevention of adhesion formation and later adhesions present at reoperation could be examined; 3) a small open-label trial in Europe of neonates undergoing staged operations focused on the reoperation occurring at 2 to 8 months after the index operation (unlike study 2, the sponsor does not tell us if a new piece of REPEL-CV was used if delayed sternal closure was necessary); and 4) the multicenter randomized pivotal trial whose details you have just heard. The pivotal trial also was in neonates who were undergoing staged reconstruction, so predictably required resternotomy.

From the trial in adults comes the one contraindication for REPEL-CV: It is not to be used for LVADs. Interestingly, a synthetic neopericardium has been said to facilitate explanting such devices.[7] Movement of the connecting grafts was said to disrupt the REPEL-CV membrane. As we all know, we are entering a new era of temporary and permanent mechanical circulatory support devices, and tomorrow's LVAD may well be a completely intravascular device. Thus, the language of the contraindication needs to be more carefully chosen.

Efficacy

Trials 2 and 3 show an evolution in grading of adhesions from coarse to finer, and a quantitative estimate of the surface area occupied by each grade of adhesion of what is called the investigational site (the extent of which may be open to interpretation). For the pivotal trial, percent of surface area occupied by severe adhesions was the primary end point. There is no mention in the materials provided how this end point was quantified in each patient, but I surmise it was a coarse visual estimate. The percents in each grade added to 100%. What we do know without question is that the distribution of values for these four additive grades demonstrated quite non-Gaussian properties. As evidence, the standard deviation of most summary mean statistics is larger than the mean. Thus, I do not know if this product did or did not meet the predefined 20% "clinically meaningful difference."

Thus, in Section 7, Table 17 on page 38, Figure 1 on p. 40, and Table 20 on p. 42 are uninterpretable by me. True, Wilcoxon tests for differences in medians are given, but is this the appropriate test, and does it address the predefined 20% reduction? Further, given the additive nature of the scale for adhesions, are independent grade-by-grade

analyses of this ordinal scale appropriate as a secondary endpoint or are there more meaningful methods of analysis?

The secondary dichotomous end points are perhaps easier to understand: Severe adhesions occurred at a substantially lower frequency in REPEL-CV patients than in control patients. What is clear from the data is that REPEL-CV is not a panacea. About a third of patients still developed severe adhesions, and either these same patients or at least a similar percentage developed the same fibrous capsule, with a focal foreign body giant cell reaction, that is typical of permanent sheets (pp. 51-52 of Section 7).

Perhaps the most perplexing secondary end point results are those of dissection time (Table 19, p. 41 of Section 7). A reason to use products to reduce adhesions is, in part, to reduce dissection time. Although not commented upon by the sponsor, in patients with either no severe adhesions or severe adhesions, dissection time was systematically longer in the REPEL-CV patients then in control patients. Why was this? Was assessment time included in dissection time, and assessment took longer in REPEL-CV patients?

Unmeasured in this trial was intraoperative blood loss, which also is an important reason to prevent adhesion formation.

Safety

These are difficult patients, with high expected mortality, complications of preoperative ischemia that increase risk of enterocolitis, and tricky balance of pulmonary and systemic blood flow in the interim between Norwood and cavopulmonary/Fontan procedures. So, it is important to set aside all these well-known, predictable complications and focus on the single most relevant safety issue: presence even temporarily of a foreign body in the mediastinum that may harbor infective agents leading to mediastinitis.

Here I am again confused by the initial data, the adjudicated data, and the raw data. In the description of serious adverse events listed in Section 9 for REPEL-CV, I think there is a definite or possible mediastinal complication in cases MW #03-03 (p. 56), ES #07-04 (p. 60), IF #07-10 (p. 61), PEH #13-09 (p. 65), KJL #16-08 (p. 70), and possibly a sterile mediastinal reaction in JAS #16-09 (pp. 70-71). Among control patients, mediastinal complications, albeit seeming to be less severe, occurred in cases KLM #01-10 (p. 73), PB #03-10 (p. 74), DH #06-07 (p. 77), and EL #16-07 (p. 86). If these events are all true mediastinal ones, they suggest similarity of mediastinal complications more strongly than the sponsor has indicated, although I emphasize that severity seems greater in REPEL-CV cases than controls.

Now, admittedly there are more foreign bodies in the mediastinum of these cases than REPEL-CV, so it is important that we have control patients to ascertain “background noise.” This can be said of all other complications, which are important to these babies and their parents, but of little or no importance in assessing safety of this product.

Finally, are there other unknowns? Yes. We do not know long-term safety effects that might become evident were this product used for adult cardiac surgery (such as patients receiving biological prostheses that will eventually require replacement if the patient survives long enough).

BENEFIT VS. RISK

In my opinion, there is clear incremental benefit of the product in terms at least of reduced substernal adhesions. I do not understand why this has not translated, however, into saving dissection time, and, in fact, seems to prolong it. The product does not

perfectly protect against adhesions, and why this is true probably cannot be ascertained from this sample.

Is it safe? We find some mediastinitis and some evidence of mediastinal inflammatory response. Probably it is more nearly equivalent to control patients than is portrayed in the tables, but this is something that should be monitored, including the degree of seriousness of the complication.

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