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TITLE: Novel Strategies to Improve Immunomodulation and Noninvasive Clinical Monitoring in VCA

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14. ABSTRACT

Safely minimizing the risks associated with vascularized composite allotransplantation (VCA) is crucial for functional restoration of wounded warriors. Our overarching goal is enabling functional and aesthetic restoration to patients with severe, unreconstructable vascularized composite tissue defects by safe VCA protocols with minimal side effects. Our specific aims are: (1) Establishing the efficacy of a low-dose IL-2 protocol at enabling minimization of immunosuppression to sirolimus monotherapy in recipients of VCA. (2) Exploring correlations between cellular and molecular immunoassays performed in specimens from VCA recipients (and their donors) with clinical observations of stability and rejection. In future trials, these assays can be developed into tools that prospectively predict rejection and tolerance in VCA, and (3) Implementing next-generation methods to supplement and potentially overcome limitations of established methods such as histology and ultrasound biomicroscopy (UBM). We are enrolling 5 subjects for VCA. <3 months after VCA, once recipient and allograft are stable, we will administer an IL-2 based protocol intended to enable minimization of immunosuppression to sirolimus monotherapy. Afterwards, immunosuppression will be weaned.

SUBJECT TERMS: NONE LISTED

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Contents

1. Introduction

Many individuals lose parts of their faces, their limbs or their abdomen in traumatic incidents such as active combat, burns, gunshot wounds, violent attacks, and motor vehicle accidents, amongst others. People with these types of traumatic injuries have decreased quality of life, and are often disabled. Although they may receive the best of the available conventional reconstruction therapies, they continue to suffer from chronic pain, psychological distress, social isolation, and limitations in their ability to perform daily activities such as bathing, dressing, ambulating, and eating without substantial help. “Vascularized composite allotransplantation”, or “VCA” for short, is a new promising therapy for these types of patients. Face transplants, hand transplants and abdominal wall transplants are examples of types of VCA.

The most significant disadvantage of VCA is that patients who receive this therapy must take immunosuppressive drugs for the rest of their lives in order to prevent their bodies from rejecting the transplant. Immunosuppressive drugs pose significant health risks. As VCA is not a life-saving therapy, the risks of immunosuppressive drugs are given much more consideration than in the case of, for example, a heart transplant. Therefore, many people who would benefit from VCA end up not receiving the therapy due to concerns about immunosuppression. We have developed a novel, safe treatment that may enable patients who receive VCA to drastically reduce or even completely eliminate immunosuppressive drugs in the months after transplantation. The objective of this study is to test this novel treatment in 5 patients who will receive VCA. At least 3 months after their VCA operations, our patients will receive our novel treatment which is based on low doses of “interleukin-2” or “IL-2” for short, over a period of 3-4 months. After receiving IL-2 treatment, we will try to minimize or possibly stop immunosuppressive drugs in our patients. If, however, we see signs of rejection, we give standard immune suppression back, which stops rejection successfully in the vast majority of VCA patients. We will follow the progress of our patients for 24 months thereafter. Using state of the art molecular, cellular and imaging technologies, we monitor the subjects’ immune status to identify patients who can safely minimize immune suppression and those who are likely to suffer rejection.

VCA will give many patients the opportunity to improve their quality of life and regain social participation and independence. Our study is carefully designed to thoroughly inform the patients about risks and benefits of participation, to minimize the incidence of complications, and if it is not possible to avoid them, have a safe treatment plan.

2. Key Words:

Vascularized composite allotransplantation, immune modulation, immune tolerance, IL-2

3. Accomplishments.

In April 2018, we we have performed a face transplant on the first patient and started the IL-2 protocol in October 2018. The patient is currently stable on IL-2 for almost a year and did not have any acute rejections nor side-effects of the immunosuppression. He receives IL-2 injections every third day and his tacrolimus levels are maintained at 6-8 ng/ml. Prednisone and mycophenolate were successfully weaned. We are continuing the IL-2 protocol in this patient given the positive preliminary results.

In July 2019, we have performed a face transplant on the second patient after being almost 1.5 years on waitlist. The surgery was successful and we expect to start IL-2 protocol in this patient in 3-4 months if no complications occur.

In the meantime, we have:

- Reported to the FDA and maintained IND approval for use of IL-2 in this patient population
- Discussed methods to recruit additional candidates

In addition, we have kept up with our monthly teleconference calls with the sponsor, as well as maintained up to date reporting requirements.

4. Impact

Active combat is inflicting multiple devastating injuries to unprotected body areas such as the face and limbs with alarming incidence, and resulting in limb amputation, facial disfigurement, and loss of abdominal wall. Conventional reconstructive surgery is limited in its ability to restore form and function after these injuries. Disability with associated long-term medical care and disability benefit costs is common. Considering the high incidence and devastating consequences of these complex injuries to American Service members, there is a clear need to improve their treatment outcomes. Vascularized composite allotransplants provide a mean to functionally and cosmetically restore these tissues; however, at the cost of lifelong immunosuppression. If successful, these studies will facilitate induction of immunologic tolerance to the transplanted tissues thus improving the rate of return to duty, deployment and function of American service members and veterans recovering

from combat-related limb loss, with associated improvements in quality of life, mental health, social participation and the American economy.

5. Changes/Problems

One of the most significant roadblocks in this project has been the slower subject recruitment than anticipated. This was due to low volume of referrals, and no military referrals. We are doing everything we can to get more patient candidate referrals. Three transplant candidates that contacted our center were not found eligible for transplant past year. Due to the slow recruitment rate we have processed a no-cost extension to extend for an additional year and this was approved in August 2018. We have advertised our study in Plastic Surgery News periodical, and will explore longer duration, as well as other professional magazines. We also reached out to our colleagues at MGH to team up in patient recruitment.

6. Products

Nothing to report at this time.

7. Publications, Abstracts and Presentations

Part of the data from the first patient will be presented at Military Health System Research Symposium (MSHRS) Conference 2019, Kissimmee, Florida, Aug 19-22.

8. Inventions, Patents and Licenses

Nothing to report at this time.

9. Reportable Outcomes

Nothing to report at this time.

10. Other Achievements

Nothing to report at this time.

11. Participant and other collaborating organizations

Our collaboration with the Massachusetts Institute of Technology remain in place and active; we have obtained ceded review from their institutional IRB so that their contribution to our studies remains under oversight by the Partners Human Research Committee. Due to the passing of our collaborator at Beth Israel Deaconess Medical Center this past year that collaboration has been terminated and the responsibilities of the BIDMC have been transferred back to Dr. Riella at BWH.

12. Special Reporting Requirements

None.

13. Appendices

None.

Novel strategies to improve immunomodulation and non-invasive clinical monitoring in VCA

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MR140159

PI: Bohdan Pomahac **Org:** Brigham and Women's Hospital **Award Amount:** $2,487,729

Study/Product Aim(s)

- SA1. To develop a safe and feasible regimen for minimization of immune suppression in recipients of VCA through daily subcutaneous low-dose rIL-2.
- SA 2. To explore correlations between cellular and molecular immune markers in VCA and clinical observations of immune stability and rejection.
- SA3. To develop non-invasive technologies to monitor for VCA rejection, such as next-generation MR methods.

Approach

Exploratory, open-label, prospective safety and feasibility clinical trial that will enroll 5 candidates for VCA.

Five subjects will be recruited and enrolled for VCA. Following VCA, they will receive an IL-2 drug protocol.

Specimens and imaging data from these VCA recipients will be used towards SA2 and SA3.

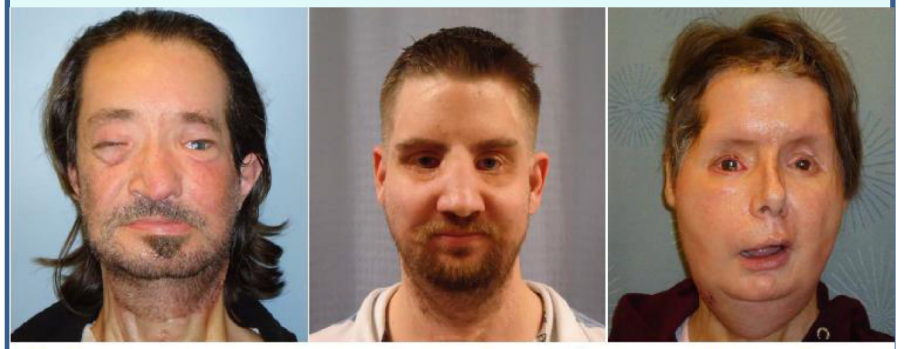

Figure 1. Post-operative frontal view of three full-facial recipients at BWH, 17 months (left), 18 months (center) and 12 months (right) after the operation.

IRB and HRPO approval obtained.

Timeline and Cost

Activities CY	15	16	17	18
Task 1. DOD and IRB approval				
Task 2. Enrollment of 5 subjects				
Task 3. VCA surgeries				
Task 4. Administration of IL-2 protocol				
Estimated Budget ($K)	**$273,737**	**$597,244**	**$597,244**	**$323,507**

Updated: August 2019

Goals/Milestones

CY17 Goal – IRB/HRPO approval
☑ Both IRB and HRPO approved
CY17 Goal – Enrollment of 5 subjects
☑ Informed consent – 2/5 subjects
☑ Screening – 2/5 subjects
CY18 Goal – VCA surgeries
☐ 5 subjects – 2/5 surgeries
CY18 Goal – Administration of IL-2
☐ In 5 subjects – 1/5 Subjects

Comments/Challenges/Issues/Concerns

- Timelines have changed with respect to the original proposal because of delays in obtaining IRB/HRPO approval as well as slow subject recruitment.

Budget Expenditure to Date

Projected Expenditure: $2,487,729
Actual Expenditure: $1,806,328