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13. SUPPLEMENTARY NOTES

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.

15. SUBJECT TERMS

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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

We continued to administer IL-2 in one patient until he was removed due to an adverse event in November 2019. We continued providing post-operative care for our other patient after his July 2019 transplant. We have also continued collecting biological samples from both patients as per Task 5 of the SOW.

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, no military referrals, and the limitations on

patient interactions due to the COVID-19 pandemic. We are doing everything we can to get more patient candidate referrals. Six candidates were found ineligible for transplant in the past year. Due to the slow recruitment rate, we have processed a no-cost extension for one year, which was approved in July 2019. 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.

Our patient who was receiving IL-2 developed hemolytic anemia in November 2019, after receiving a low, stable dose for over a year with no side effects. The patient stopped taking IL-2 and was switched to Prednisone. Since we were unable to determine the cause of the anemia, the patient was removed from the study.

Our other post-transplant patient is not yet eligible to receive IL-2 due to the presence of De Novo donor specified antibodies (DSAs) during biopsies.

6. Products

Nothing to report at this time.

7. Publications, Abstracts and Presentations

Part of the data from the first patient was 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

Dr. Riella has accepted a new position at Massachusetts General Hospital. He has been replaced by Dr. Jamil Azzi, who has taken over his lab and all associated tasks for this project.

12. Special Reporting Requirements

None.

13. Appendices

None.