

Vascularized Composite Allotransplantation

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Disclosures

- Medical Science Liaison, Takeda Pharmaceuticals

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Learning Objectives

- Compare and contrast vascularized composite allotransplantation (VCA) to other solid organ transplants (SOT)
- Design an induction, maintenance, and acute rejection immunosuppressive pharmacotherapeutic plan for VCA recipient
- Consider patient-specific factors in selection of immunosuppressive regimen and improving adherence

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History of VCA

- 1954 – First attempt of hand transplant (Ecuador)
- 1998 – First successful hand transplant (France)
- 1999 – First hand transplant in the US (Jewish Hospital, KY)
- 2005 – First successful partial face transplant (France)
- 2008 – First partial face transplant in the US (Cleveland Clinic, OH)
- 2010 – First successful full face transplant (Spain)
- 2011 – First full face transplant in the US (Brigham and Women's Hospital, MA)
- 2018 – First (and only) face re-transplant (France)

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Current State of VCA

- Voluntary Reporting to the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) as of 2019
 - 74 Upper Extremity Transplants (31 unilateral and 43 bilateral)
 - 31 Face Transplants
- Complication similar to those reported in Solid Organ Transplantation
- Upper Extremity Transplant (UET) patient survival was 96.7% at 10 years, with graft survival of 86.6%
- Face Transplant (FT) patient and graft survival was 96.2% at 5 years

Petruzzo, P. Curr Transplant Rep. 2019

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Current State of VCA

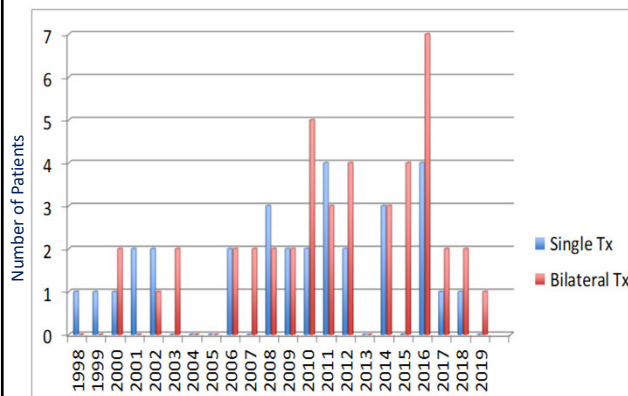


Figure 1: Upper Extremity Transplants reported to IRHCTT

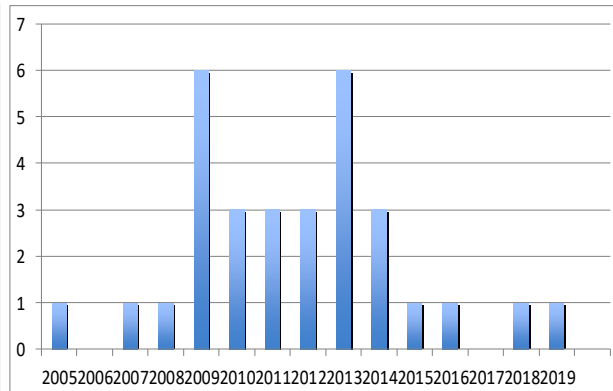


Figure 2: Face Transplants reported to IRHCTT

Adapted from Petruzzo, P. Curr Transplant Rep. 2019

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Consideration for Listing / Transplantation

- Absolute inclusion and exclusion criteria has not been established
 - Center specific criteria and used of tools, such as The Cleveland Clinic FACES Score
- Defects impairing not only appearance but also critical functions which are difficult to restore with conventional reconstruction techniques
- Considered to be life enhancing procedure
- Patient must understand the risks of lifelong immunosuppression
- Generally, candidates are physically healthy, but many have psychiatric disorders associated with their trauma
 - Center specific assessment of psychiatric health (i.e. The Innsbruck Psychological Screening Program for Reconstructive Transplantation)
- Other considerations for transplantation: skin tone, gender and age matched to recipient

Chim, H. Mayo Clin Proc. 2014

Tasigiorgos, S. Transpl. Int. 2018

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Pre-Transplant Non-pharmacological Considerations

- Psychiatric disorders related to injuries
 - 2/3 of FT patients suffered from ballistic injuries or burns
 - Patient with chronic pain and multiple reconstructive surgeries
 - Increased risk of estrangement to society
 - Increased risk of addiction and substance abuse
- Limited experience with chronic medication regimen and low health literacy
- Complicated support system
- Financial hardship after trauma
- Blindness, difficulty swallowing and lack of fine motor skills

Chim, H. Mayo Clin Proc. 2014

Tasigiorgos, S. Transpl. Int. 2018

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Pharmacological Considerations

- Induction Regimens for Upper Extremity Transplant
 - 57.9% Anti-Thymocyte Globulin
 - 22.6% Anti-CD52
 - 23.2% IL-2 Inhibitor
- Induction Regimens for Face Transplant
 - 91.7% Anti-Thymocyte Globulin
 - 8.1% IL-2 Inhibitor
- Intraoperative corticosteroids 500-2000mg used in 97% of VCA transplants

Petruzzo, P. Curr Transplant Rep. 2017

Tasigiorgos, S. Transpl. Int. 2018

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Pharmacological Considerations

- | | |
|--|---|
| <ul style="list-style-type: none"> • Maintenance Regimen in UET <ul style="list-style-type: none"> – Calcineurin inhibitors <ul style="list-style-type: none"> – 94.8% Tacrolimus <ul style="list-style-type: none"> – Targeted troughs 4 -15ng/mL – Antimetabolites <ul style="list-style-type: none"> – 91.2% Mycophenolate Mofetil – Corticosteroids (87.5%) – Mammalian Target of Rapamycin (9.8%) – Costimulation Blocker (4.5%) | <ul style="list-style-type: none"> • Maintenance Regimen in FT <ul style="list-style-type: none"> – Calcineurin inhibitors <ul style="list-style-type: none"> – 100% Tacrolimus <ul style="list-style-type: none"> – Targeted troughs 10-15ng/mL for month 1-6 and 8-10 ng/mL thereafter – Antimetabolites <ul style="list-style-type: none"> – 95.7% Mycophenolate Mofetil (500-3000mg daily) – Corticosteroids (95.7%) – Mammalian Target of Rapamycin (6.6%) – Costimulation Blocker (3.3%) |
|--|---|

Chim, H. Mayo Clin Proc. 2014

Lantieri, L. Lancets. 2016

Petruzzo, P. Curr Transplant Rep. 2017

Tasigiorgos, S. Transpl. Int. 2018

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Pharmacological Considerations

- Antimicrobial Prophylaxis in UET
 - 76.4% Anti-Cytomegalovirus prophylaxis
 - 77.4% Antifungal prophylaxis
 - 79.2% *Pneumocystis jirovecii* prophylaxis
- Antimicrobial Prophylaxis in FT
 - 91% Anti-Cytomegalovirus prophylaxis
 - 67.7% Antifungal prophylaxis
 - 87% *Pneumocystis jirovecii* prophylaxis

CMV prophylaxis is typically used for 3 to 6 months post transplant

No consensus on type and length of fungal prophylaxis

PCP prophylaxis is typically used for 6 to 12 months post transplant

Petruzzo, P. Curr Transplant Rep. 2017

Tasigiorgos, S. Transpl. Int. 2018

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Pharmacological Considerations

Table 2 Complications in UET

Complications (%)	First post-transplant year	Follow-up
Opportunistic infections		
Bacterial infection	32	7.7
Cytomegalovirus infection	12	1.5
Herpes simplex infection	6	—
Herpes zoster infection	2	9.2
Epstein-Barr virus infection	—	1.5
Fungal infection	12	1.5
Metabolic complications		
Hyperglycemia/Post-transplant Diabetes Mellitus (PTDM)	42	23
Increased creatinine values	25	26
Arterial hypertension	6	11
Malignancies	2	3

Table 6 Complications in face allotransplantation

Complications (%)	First post-transplant year	Follow-up
Opportunistic infections		
Bacterial infection	24.1	13.8
Cytomegalovirus infection	13.8	6.9
Herpes simplex infection	17.2	13.8
Herpes zoster infection	—	—
Epstein-Barr virus infection	3.4	—
Fungal infection	17.2	6.9
Metabolic complications		
Hyperglycemia/Post-transplant Diabetes Mellitus (PTDM)	24.1	3.4
Increased creatinine values	44.8	13.8
Arterial hypertension	3.4	10.3
Malignancies	3.4	13.8

Adapted from Petruzzo, P. Curr Transplant Rep. 2017

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Pharmacological Considerations

- Rejection
- 2007 Banff VCA working classification
 - Acute Cellular Rejection
 - Concern of high sensitization
 - Most rejections responsive to bolus systemic steroids
 - Antibody Mediated Rejection
 - Single case of AMR reported in highly sensitized (cPRA 98%) FT patient which was successful treated
 - Chronic Rejection
 - Significantly less frequent complication than predicted, only 2 cases reported

Cendales, LC. Am J Transplant. 2008

Chim, H. Mayo Clin Proc. 2014

Chandraker, A. Am J Transplant. 2014

Schnider, M. Transp. Int. 2016

Tasigiorgos, S. Transpl. Int. 2018

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Pharmacological Considerations

- Novel Therapies
 - Topical products: the effect of topical agents (CNIs and glucocorticoids) is inconclusive
 - Localize delivery systems
 - Inducing tolerance and minimizing lifelong immunosuppression
 - Microchimeric induction through simultaneous bone marrow transplantation
 - Development of anti T-cell antibodies, or stem cell therapies

Chim, H. Mayo Clin Proc. 2014

Schnider JT. Clin and Develop Immunology. 2013

Taddeo, A. Curr Opin Organ Transplant. 2018

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Non-Pharmacological Consideration

- Noncompliance
- Blindness
- Nerve Regeneration
- Renal function deterioration
- Malignancies
- Revision surgeries (average 1-6 surgeries post transplant)
- Non-invasive monitoring and diagnosis of rejection
- Inconsistent outcome reporting

Chim, H. Mayo Clin Proc. 2014
 Petruzzo, P. Curr Transplant Rep. 2017
 Tasigiorgos, S. Transpl. Int. 2018

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Other Areas of VCA

- 1996 – First Allogenic Vascularized Knee Transplant
- 2003 – First Abdominal Wall Transplant
- 2006 – First unilateral lower limb allotransplant (between 3mo old ischiopagus conjoined twins)
- 2010 – First successful uterus transplant
- 2011 – First successful bilateral lower limb transplantation
- 2014 – First baby born to uterus transplant recipient
- 2014 – First successful penis transplant

Chim, H. Mayo Clin Proc. 2014
 Diefenbeck, M. Transp. Int. 2007
 van der Merwe, A. Lancets. 2017

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Question 1: Face Transplant recipients have comparable rates of acute rejection (AR) during the first year post-transplant to kidney transplant recipients:

- A Yes, 15% of all face transplant recipient experience AR, compared to 13% of kidney transplant recipients
- B Yes, 90% of all face transplant recipient experience AR, compared to 85% of kidney transplant recipients
- C No, 15% of all face transplant recipient experience AR, compared to 85% of kidney transplant recipients
- D No, 90% of all face transplant recipient experience AR, compared to 13% of kidney transplant recipients

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Question 2: Which of the following is the best treatment option for unilateral hand transplant recipient diagnosed with Banff grade 2-3 acute rejection:

- A No treatment is required, continue to visually monitor the allograft and consider therapy when visible lesions appear
- B Initiate mTOR inhibitor (sirolimus) to augment immunosuppression and prevent chronic vasculopathy
- C Methylprednisolone pulse of 500mg daily x3 doses, plus topical clobetasol daily for augmentation of therapy
- D Initiate topical tacrolimus 2 times daily for 14 days

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Question 3: Blindness is absolute contraindication to face transplant:

- A Yes, all centers consider blindness an absolute contraindication transplant due to poor adherence post-transplant
- B Yes, blind face transplant recipients did not report improvement in quality of life as they are not able to visualize it
- C No, a number of pre-transplant blind candidates were transplanted with no difference in outcomes
- D No, face transplant candidates gain back sight after the procedure

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Key Takeaways

- The goal of VCA is to improve patient's quality of life including functional recovery and patient well-being
- Patients' compliance to the immunosuppressive regimen and to the rehabilitation programs plays important role
- Inconsistencies and discussion exist in regards of classification of Acute and Chronic Rejections
- The current state of VCA is limited by the lack of reporting and incomplete data available

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