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Animal Models and Immunosuppressive Regimens in Vascularized Composite Allotransplantation – A Review

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Review Article

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Abstract

Introduction: The development of vascularized composite allotransplantation (VCA) and its clinical need has led to the need for more animal models to study and perform the research required to further this specialty in terms of functional recovery and immunomodulatory improvements. Much of the animal models are reported in individual series in the literature but there has not been a systematic review as such of these models. Here we present a compilation of the animal models reported in the literature thus far in VCA.

Material and methods: A systematic review of the literature was performed for any studies which involved the use of animal models in various aspects of VCA research. The models were organized according type of VCA transplant, whether they were orthotopic or heterotopic, immunosuppressive regimen each study used and investigation purpose.

Results: 21 facial transplant models were reported, 3 abdominal wall transplants, 4 penile transplantations, 21 uterus transplantations, 12 hindlimb transplantations and 4 myocutaneous flap transplantation animal models were reported. Primates, swine, rats, mice, rabbits, sheep and dog animal models in VCA were also reported.

Discussion: The review of existing animal models will allow further research to be focused in other areas of VCA where there is a current paucity of literature. The immunosuppressive regimens used in each animal model can also be reviewed to determine which regimen works in which type of animal model which will save time and resources for future research.

Keywords: Animal Models; Vascularized Composite Allotransplantation (VCA)

Abbreviations: VCA: Vascularized Composite Allotransplantation; SOT: Solid Organ Transplantation; CTA: Composite Tissue Allotransplantation; IRHCTT: Registry on Hand and Composite Tissue Transplantation; ATG: Anti-thymocyte globulin.

Introduction

Vascularized composite allotransplantation (VCA) is an up and coming clinical modality in the realm of reconstructive microsurgery. Being able to replace tissues like for like *en bloc* is absolutely crucial and empowers the surgeon to achieve the most optimal outcome. However, the greater goal of VCA is the ability of the reconstructive surgeon to not only restore form but also function. Functional restoration could arguably be the epitome of reconstruction where the quality of lives are improved not only from external appearance but rather also allow the patients to make gainful recovery of lost body parts that are crucial to the activities of daily living.

Trauma remains a significant burden in today's society with many resulting in soft tissue defects. Other causes of soft tissue defects include congenital deformities and neoplastic conditions. Much of the previous methods for reconstruction include prosthesis or sequential flaps that obliterate and attempted to restore the form of a tissue defect. However, this is often inadequate and is lacking in function. VCA differs from solid organ transplantation (SOT) where tissues of varying antigenicity are transplanted *en bloc.* This results in issues of varying rejection rates. In particular, skin which is often a component of VCA transplants such as the hand and face has the highest antigenicity of all body tissue types. As such, rejection faced by skin component is high and the recipient or patient is dependent on a high constant level of immunosuppression. Skin contains dendritic cells such as Langerhans cells that have strong immunogenic properties and it has been shown that some of these cells of donor origin reside in the epidermis decades after the transplantation [1,2].

Chronic immunosuppression itself carries deleterious effects in the long run where patients face opportunistic infections and an increased risk of malignancy from the decreased immunity that is usually present to prevent and take on a surveillance role. As such, one has to deliberate the actual pro and cons when deciding the perform VCA on a patient. The patient should also be able to finance a lifelong requirement of immunosuppressive drugs which are often costly and have a high dropout rate due to the side effects.

Much of the research at present in VCA is on better improving the safety profile of such procedures, especially with the need for the improvement in immunosuppressive regimens. By decreasing our reliance on immunosuppressive drugs, we increase the universal acceptability of such a procedure. The ultimate goal in transplant science would be to achieve allograft tolerance. Tolerance to an allograft is a phenomenon where the recipient body does not recognize the foreign antigens from the donor and hence will accept the graft. Immunosuppressive drugs can hence be reduced or even omitted. In order for this process to occur, immunological manipulation and re-education of the recipient's immune system has to occur. Several strategies already show promise in this respect and will be discussed as part of this study. Varying tissue types also have varying levels of inducibility with regards to tolerance formation. In particular, due to the varying tissue types of differing antigenicity in VCA, tolerance is often difficult to achieve.

A Brief History of VCA

VCA has come a long way since its first conception back in AD 348. It has always been a goal of mankind to be able to replace like with like where allograft transplantation *en bloc* of a gangrenous leg of an elder church sacristan was performed by two brothers known as the miracle of Cosmas and Damian [3]. Previously known as composite tissue allotransplantation (CTA), VCA in the past started off with transplantation between identical twins which obviated the need for immunosuppression, which is the bane of VCA and is a focus of intense research at present.

The first hand allotransplantation was performed in 1964 in Ecuador where a first generation drug regimen was provided. This included steroids and azathioprine initially. However, the hand allograft still was rejected 2 weeks later. Allografted tendons had been performed using non vascularized techniques to replace lost or nonfunctional upper extremity flexor tendons but end results were unacceptable due to the lack of viability of the grafts resulting in rupture as well With the limited knowledge in immunological manipulation and the adverse effects that happened, further VCA cases were put on hold. It was not till the discovery and development of cyclosporine A during kidney transplantation that it was applied to VCA in the 1980s where immunosuppression finally became more effective. The first successful hand transplant then was carried out in 1998 in France. However, the patient refused to adhere to the immunosuppressive regimen due to personal reasons and compliance issues and hence the arm was again amputated almost 3 years after surgery. The first vascularized tendon was performed by Guimberteau

where two allotransplantations of digital flexor tendon apparatus were collected from a living nonrelated donor and from a deceased donor [4]. The tendons were then revascularized using the recipient's ulna vessels and ultimately received acceptable using multiple doses of cyclosporine A [5]. The first successful face transplant occurred in 2005 and since then, several countries have followed suit [6].

An Overview of Clinical VCA Cases to Date

Various specialized centers in the world with the capability and infrastructure in performing VCA should perform this. An important source of data is the International Registry on Hand and Composite Tissue Transplantation (IRHCTT), which is a voluntary registry that collects clinical information on VCAs. The most recent report of the IRHCTT was published in 2010 and provides follow-up data on 49 hand transplants in 33 patients. Thus far, there have been 89 hand transplants performed since 1998. The United States currently has the largest number of cases, followed by China and Poland.

Types of VCA Animal Models Reported

Face Transplant Models

A variety of animal models have been used in VCA experiments with the majority being orthotopic face transplants. The animal models were performed in animals such as primates, swine, sheep, canine, rabbit, rats and mice. Different compositions of face allograft comprising of bone, nerve and soft tissue in each animal model have been reported in the literature which has varying levels of antigenicity. As such, each report has used varying types of immunosuppression, which is also dependent on the response of each animal type and to the type of immunosuppressive drug. The transplantation of each allograft can be considered orthotopic if the graft replaces the original site of the donor i.e. the face, or heterotopic if the allograft is placed in a distant site different from the original area. Orthotopic transplants in these animal models are mostly for assessing not only the rejection process but also the functional restoration of the allograft. Heterotopic allografts, however, are used more for assessing the degree of rejection but normally do not carry an assessment of functional recovery.

In a primate model, heterotopic transfer of a facial transplant including the mandible were transferred from MHC mismatched M Fascicularis monkeys. Anti-thymocyte globulin (ATG) was used as an induction regimen with Tacrolimus and Rapamycin in combination as a maintenance regimen.

Two reports using swine and sheep models were used with facial allografts including bone. However, no immunosuppressions was used in these models and were more for the surgical technique of producing such models.

Four canine models were used in mismatched donors to beagle dog recipients. All reports were orthotopic and involved a hemifacial transplantation. With these reports, 2 reports utilized ciclosporin and steroids as maintenance immunosuppression. 2 other reports used tacrolimus as maintenance immunosuppression and with one report using tacrolimus only for 7 days. One report in a rabbit model used a face and scalp transplantation model with no immunosuppression.

11 rat animal models for face transplant were reported in the literature. 9 of the reports were allografts and 2 were syngeneic. 10 reports were orthotopically transferred and 1 with heterogenic transplantation. Various face transplant components were reported ranging from ear, scalp, face, mystacial pad or mandible with tongue transplantation. A combination of ciclosporin A or tacrolimus was used in these animal models. 4 of these reports had nerve coaptation which looked at the functional recovery in allograft especially using mystacial pad transplantation.

2 reports of murine orthotopic face transplant were reported with either a hemiface or ear allograft. No immunosuppressive regimens were used in these reports with more focus on the surgical technique of transferring an ear or hemiface. The information is presented in the table 1.

	Allo-transplantation	Approach	Graft	Regimen	Reference
Primate	Mismatched donor to recipient M. Fascicularis monkey	Heterotopic	Mandibular OMC	ATG (10 to 20 mg/kg/d) induction with Tacrolimus (0.2 to 0.1 mg/kg/d) and Rapamycin (0.05 incresased to 0.2 mg/kg/d) maintenance.	[7]
Swine	Pig autotransplant	Orthotopic	Le-Fort-based maxilloface	No immunosuppression	[8]

Sheep	N/A	N/A	Hemifacial and auricle	N/A	[9]
Canine	Mongrel to Beagle dog	Orthotopic	Hemiface and scalp	CSA (6-18 mg/kg/d) and steroid methylprednisolone (4-8 mg/kg/d).	[10]
Canine	Mismatched donor to recipient Beagle dog	Orthotopic	Hemiface and scalp	Tacrolimus 2 mg/kg/d for 7 days.	[11]
Canine	Mismatched donor to recipient Beagle dog	Orthotopic	Hemiface	CSA (4 mg/kg/d)	[12]
Canine	Mismatched donor to recipient Beagle dog	Orthotopic	Mandibular hemijoint	Tacrolimus 1 mg/kg/d maintenance.	[13]
Rabbit	NZB to NZW	Orthotopic	Facial and scalp	No immunosuppression	[14]
Rat	BN to LEW	Orthotopic	Mystacial pad	CSA 16 mg/kg on POD 1-14, 13 mg/kg on POD 15-80, then 10 mg/kg maintenance.	[15]
Rat	BN to LEW	Orthotopic	Face and scalp	CSA 16 mg/kg/day, tapered to 2mg/kg in 4 weeks and maintained.	[16]
Rat	LEW Syngeneic	Heterotopic	Hemiface with mandible and Tongue	No immunosuppression	[17]
Rat	BN to LEW	Orthotopic	Auricle	CSA 16 mg/kg/d for 2 wks and tapered to 8 mg/kg/d for 2 wks.	[18]
Rat	BN to LEW	Orthotopic	Hemifacial with mystacial region	Tacrolimus 8 mg/kg/d, tapered to 2 mg/kg/d in 4 weeks.	[19]
Rat	BN to Wistar	Orthotopic	Hemiface	CSA 16 mg/kg/d for 7 days, tapered to 2 mg/kg/d for 23 days.	[20]
Rat	BN to LEW	Orthotopic	Auricle	CSA 16 mg/kg/d in first week, tapered to 8 mg/kg/d and maintained for 2 wks, then 4 mg/kg maintained.	[21]
Rat	LEW Syngeneic	Orthotopic	Ear	No immunosuppression	[22]
Rat	Lew-BN to Wistar-Lew	Orthotopic	Mystacial pad	Tacrolimus 6 mg/kg/d in first wk, tapered to 4 mg/kg/d in second wk, then 2 mg/kg/d maintained.	[23]
Rat	Lew-BN to LEW	Orthotopic	Hemiface with ear and scalp	CSA 16 mg/kg/d in first wk, tapered to 2 mg/kg/d over 4 wks and maintained.	[24]
Rat	BN to LEW	Orthotopic and Heterotopic	Hemiface and scalp	CSA 8 mg/kg on POD 1–2, 6 mg/kg on POD 3–6, 4 mg/kg on POD 7–30, 2 mg/kg on POD 31–42.	[25]
Murine	BALB/c to B6	Orthotopic	Myocutaneous hemiface	No immunosuppression	[26]
Murine	BALB/c to B6	Orthotopic	Ear	No immunosuppression	[27]

Table 1: Facial animal models.
1. NZW: New Zealand White; NZB: New Zealand Black; BN: Brown Norway; LEW: Lewis; B6: C57BL/6
2. CSA: Cyclosporin A; ATG: Anti-thymocyte globulin.
3. OMC: Osteomyocutaneous.

Abdominal Wall Transplantation Models

Abdominal wall transplantation comprising of various tissue types also constitutes a vascularized composite allotransplantation model. All reported models thus far have been carried out in rats across MHC mismatched rats from Brown-Norway to Lewis rats. The abdominal wall transplants were orthotopic with two hemi-abdominal wall transplants and one with the inclusion of a hindlimb transplant. One report had a total abdominal wall

allograft transplanted. Anti-lymphocyte serum was used in 2 of the reports for induction therapy. Two reports utilized ciclosporin and one in combination with adipocyte derived stem cells intravenously. The models do not include all nerve anastomoses and mixed chimerism all at once. The information is presented in the table 2.

	Allo-transplantation	Approach	Graft	Regimen	Reference
Rat	BN to LEW	Orthotopic	Hemi-abdominal	ALS 2.5 mg induction, each CSA 16, 10 and 5 mg/kg/d for 10 days.	[28]
Rat	BN to LEW	Orthotopic	Total abdominal wall	Tacrolimus 0.5 mg/kg/d maintained.	[29]
Rat	BN to LEW	Orthotopic and Heterotopic	Hemi-abdominal with hindlimb	ALS 2.5 mg induction, CSA 16 mg/kg/d for 10 days and 3 doses of ADSC ($2x10^6$).	[30]

Table 2: Abdominal wall animal models.
ALS: Antilymphocyte serum; ADSC: Adipose-derived stem cell

Penile Transplantation Models

Penile allograft transplantation models have been described in 4 articles, all of which have been performed in rats. 2 studies were syngeneic rats, one of which was orthotopic and one heterotopic. These studies were focused on the surgical model and being syngeneic grafts, no immunosuppression was used. Anastomosis of the penile artery and vein was key in each model and ensuring the conduit of the urethra was restored. The other two studies used allografts and heterotopically transplanted penile grafts. One of the studies used tacrolimus and the other ciclosporin A. The information is presented in the table 3.

	Allo-transplantation	Approach	Graft	Regimen	Reference
Rat	SD19 autotransplant	Original rgion	Penis	No immunosuppression	[31]
Rat	SD19 autotransplant	Transferred to groin region	Penis	No immunosuppression	[32]
Rat	BN to LEW	Heterotopic	Penis	Tacrolimus 0.6 mg/kg/d maintained.	[33]
Rat	Lew-BN to LEW	Heterotopic	Penis	CSA 16 mg/kg/d tapered to 2 mg/kg/d in 4 wks, then maintained.	[34]

Table 3: Penile animal models.
SD 19: Sprague-Dawely rats.

Uterus Transplantation Models

Uterus transplantation has been touted as a method of restoring fertility but functionally must perform as required. 3 articles report uterus transplantations in primates, 7 in sheep, 2 in rabbits, 6 in rats and 3 in murine models. The function of the transplanted uterus was tested in rabbits, rats and mice which were successful in three of the studies. In primate uterus transplantation, various types of immunosuppressive regimens were used including tacrolimus, mycophenolate mofetil and methylprednisolone as maintenance regimes. Another protocol utilized ATG as an induction agent followed by tacrolimus and corticosteroids as maintenance. The information is presented in the table 4.

	Allo-transplantation	Approach	Graft	Regimen	Reference
Primate	M. Fascicularis monkey autotransplant		Uterus	No immunosuppression	[35]
Primate	Mismatched M. Fascicularis monkey	Orthotopic	Uterus	Tacrolimus 0.3 mg/kg/d, MMF 20-10 mg/kg/d, and methylprednisolone 10-2 mg/d maintained.	[36]

Primate	Mismatched olive baboons	Orthotopic	Uterus	ATG 10 mg/kg induction, followed by Tacrolimus 0.1 mg/kg/d, Corticosteroids 60-5 mg/kg and MMF 50 mg/kg.	[37]
Sheep	Swedish wool sheep autotransplant	Orthotopic	Uterus	No immunosuppression	[38]
Sheep	Sheep autotransplant		Uterus	No immunosuppression	[39]
Sheep	Sheep autotransplant	Orthotopic	Uterus	No immunosuppression	
Sheep	Mismatched sheep	Heterotopic	Whole uterus	No immunosuppression	[40]
Sheep	Mismatched Romney Marsh sheep	Orthotopic	Uterus	CSA 2-5 mg/kg/d maintained and prednisone 2 mg/kg/d for 2 wks.	[41]
Sheep	Mismatched sheep	Orthotopic	Uterus	ATG 50 mg induction, followed by Tacrolimus 0.02 mg/kg/d, methylprednisolone 40 mg/d and MMF 1.5 g/d.	[42]
Sheep	Mismatched Limousine sheep	Orthotopic	Uterus	CSA 10 mg/kg/d and MMF 3 g/day, both on POD 7, 14, 28, 42, 56, methylprednisolone 40 mg on POD1-7.	[43]
Rabbit	NZW allotransplant	Orthotopic	Uterus	Prednisolone 10 mg was given for 3 days following the 'spikes' alongside an increase in Tacrolimus dose from 500 mg to 1 g twice/day.	[39]
Rabbit	Mismatched NZW	Orthotopic	Uterus	Tacrolimus 500 µg twice daily postoperatively. Embryo transfer.	[44]
Rat	LEW Syngeneic	Heterotopic	Uterus	No immunosuppression	[45]
Rat	LEW Syngeneic	Orthotopic	Uterus	No immunosuppression	[46]
Rat	BN to DA	Heterotopic	Whole uterus and ovaries	No immunosuppression	[47]
Rat	BN to LEW	Orthotopic	Uterus	CSA 10 mg/kg/d maintained.	[48]
Rat	BN to LEW	Orthotopic	Uterus	Tacrolimus 0.5 mg/kg/d pump maintained.	[49]
Rat	Virgin Dark Agouti to virgin LEW.	Orthotopic	Uterus	Tacrolimus 0.5 mg/kg/d maintained. Male SD rats of proven fertility were used for mating.	[50]
Murine	F1-hybrids of inbred female C57BL/6 X CBA/ca Syngeneic	Heterotopic	Right uterine horn and the cervix	No immunosuppression Embryo transfer.	[51]
Murine	B6 Syngeneic	Orthotopic	Ovarian	No immunosuppression	[52]
Murine	F1-hybrids of C57BL/6 X CBA/ca to B6	Heterotopic	Right uterine horn and the cervix	CSA 20 mg/kg/d	[53]

Table 4: Uterus Animal Models.
1. DA: Sprague-Dawley
2. MMF: Mycophenolate Mofetil

Hindlimb Transplantation Models

Hindlimb transplantation has been a model to mimic hand transplantation where components of bone, muscle, nerve, fat and skin are included in a hindlimb. The animal models demonstrated here to explore the feasibility of modulating the immunosuppressive regimen in improving the viability of hindlimb transplants. When transplanted orthotopically, they also serve as a model to assess the functional recovery of the hindlimb when used for gait. The nerve recovery is crucial in improving the function of the transplanted allograft. The information is presented in the table 5.

	Allo-transplantation	Approach	Graft	Regimen	Reference
Primate	Mismatched donor to recipient M. Fascicularis monkey	Orthotopic	Sensate osteomyocutaneous radial forearm flap	Tacrolimus 1 mg/kg and mycophenolate mofetil 20 mg/kg Both every 12 hr, methylprednisolone 15 mg/kg for 3 days followed by 7.5 mg/kg for 2 days and a 50% reduction every 2 days until the dose was 1 mg/kg.	[54]
Swine	White pig autotransplant	Heterotopic	Whole forelimb	No immunosuppression	[55]
Swine	Mismatched newborn swine	Heterotopic	Newborn knee	No immunosuppression	[56]
Swine	Mismatched donor to recipient pigs	Heterotopic	Skeletal graft consisting of the tibia, fibula, knee joint, distal femur, and surrounding muscles	No immunosuppression	[57]
Swine	Mismatched donor to recipient pigs	Orthotopic	Osteomyocutaneous forearm flap	No immunosuppression	[58]
Swine	Mismatched donor to recipient pigs	Orthotopic	Radial forelimb osteomyocutaneous flap	No immunosuppression	[59]
Rabbit	NZW autotransplant	Orthotopic	Whole knee joint	No immunosuppression	[60]
Rat	N/A	N/A	Cremaster muscle and pubic bone flap	N/A	[61]
Rat	ACI to WF	Heterotopic	Hindlimb osteomyocutaneous	TBI 600 cGy prior to 1 dose of BMC $100x10^6$ cells/kg with Tacrolimus 1 mg/kg/d for 10 days and ALS 5 mg on POD10.	[62]
Rat	WF to LEW	Orthotopic	Simultaneous dual-surgeon hindlimb	No immunosuppression	[63]
Rat	BN to LEW	Orthotopic	Vascularized elbow	CSA 16 mg/kg/d for first wk, tapered to 2 mg/kg/d, then maintenance.	[64]
Rat	Lewis-BN to LEW	Orthotopic	IBOMC flap	CSA 16 mg/kg/d in 1st wk, tapered to 8 mg/kg/d in 2nd wk, to 4 mg/kg/d in 3rd wk and to 2 mg/kg/d in 4th wk and maintained.	[65]

Table 5: Hindlimb Animal Models.
1. WF: Wistar-Furth
2. BMC: Bone marrow cells
3. IBOMC: Iliac bone osteomusculocutaneous

Myocutaneous Tissue Transplantation Models

Soft tissue alone with varying tissue types including fat, connective tissue and muscle are collective known as myocutaneous flaps in free flap transplantation. The varying antigenicity of the tissue types is what constitutes the unique response directed against vascularized composite allotransplantations. Two swine models were reported with the use of gracillis myocutaneous flaps and fasciocutaneous flap transfers. One study had no immunosuppression and another had total body radiation with Ciclosporin-A maintenance therapy. One study utilized the transfer of the rectus abdominus myocutaneous flaps in syngeneic beagles without any

immunosuppression as a model. One study utilized a combination of heart transplantation with an abdominal musculocutaneous flap. The combination of two models is particularly interesting which confers a high degree of morbidity in the animal. In the rat study, maintenance was carried out with ciclosporin A after the inclusion of the heart transplantation. The information is presented in the table 6.

	Allo-transplantation	Approach	Graft	Regimen	Reference
Swine	Mismatched donor to recipient MGH Miniature Swine	Heterotopic	Gracilis myocutaneous flap	No immunosuppression	[66]
Swine	Mismatched donor to recipient MGH Miniature Swine	Heterotopic	Fasciocutaneous flap	TBI 100 cGy and CD3-IT conditioning prior to 3 doses of HCT $15x10^9$ cells/kg with CSA (target trough 400-800 ng/mL) for 45 days.	[67]
Canine	Beagles autotransplant	Transferred to groin region	Myocutanenous rectus flap	No immunosuppression	[68]
Rat	WKY heart and LEW VCA to F344	Heterotopic heart and orthotopic VCA	Heart and abdominal musculocutaneous flap	CSA 5 mg/kg/d every other day for 10 days after heart transplant.	[69]

Table 6: Myofasciocutaneous Animal Models.
1. TBI: Total body irradiation; CD3-IT: CD3-Immunotoxin
2. HCT: Hematopoietic cell transplantation
3. F344: Fischer 344; WKY: Wistar Kyoto

Discussion

The summary of the findings in this article demonstrates the various VCA models reported in the literature before. In order to carry our further experiments and determine the future of allotransplantation, animal models summarized in this article will hopefully shed light on the future directions for research and where further focus can be emphasized. Experimental animal surgical models can be difficult to perform and such research in VCA should be best collaborated with both clinicians and surgeons who can perform the difficult animal models, as well as basic scientists to further developments in this specialty.

Many of the immunosuppressive regimens used thus far involve an induction agent such as anti-thymocyte globulin or total body radiation which preconditions the host's immune system in preparation for a chance of engraftment of donor antigens. In particular, the phenomenon of chimerism is particularly seen in VCA research where the transfer of vascularized bone marrow, in long bones in particular, mediates a constant exchange of cells such as regulatory T cells which serve to protect the allograft. They mediate and protect the allograft from being attacked by host defense mechanisms which would destroy the graft otherwise.

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