Vascularized Composite Allotransplantation—An Emerging Concept for Burn Reconstruction

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Vascularized composite allotransplantation (VCA) has demonstrated utility in the reconstruction of extensive soft-tissue defects following severe burns. However, pre-VCA events such as multiple transfusions, previous transplantation and pregnancies, the use of skin allografts, and mechanical support devices may result in sensitization and ultimately exclude a burn patient, who may benefit most through VCA, from a hand or face transplant. The authors sought to identify the immunologic challenges involved. All reported VCA cases up to July 2016 were reviewed. Relevant data analyzed include patient demographics, burn etiology, type and extent of VCA performed, pretransplant panel reactive antibody (PRA) status, extent of human leukocyte antigen (HLA) mismatch between donor and recipient, and immunologic outcomes. Of the 142 known cases of VCA to date, 30 (mean age = 36 years) were performed for burn reconstruction (mean interval to surgery = 8.3 years). Thermal and electrical burns were most common and performed in 20 and 30% of all reported upper extremity and craniofacial VCA cases, respectively, despite highly variable pretransplant PRA (0–98%). HLA-matching statuses between donors and recipients varied from 2/6 to 6/6. No obvious relationship could be observed between the incidence and severity of acute rejection with the patient's PRA and HLA-matching statuses, although more extensive treatment was required to reverse rejection episodes in sensitized patients (PRA > 0%). Further development and refinement of clinically relevant immunomodulatory protocols is required to achieve immunosuppression minimization and/or successful transplantation tolerance to enable long-term survival of both the VCA itself and the patient. (J Burn Care Res 2017;XXX:00–00)

Survival after massive burn injuries has improved significantly during the past three decades through better intensive care management.[1] Attention has now shifted toward optimizing functional and aesthetic outcomes as part of the rehabilitative phase in burn treatment.[2] The prevalence of burn patients requiring secondary reconstructive surgery has not been well studied, with recent estimates ranging from 5.3% for facial burns at 2-year follow-up[3] to 13% at up to 10-year follow-up.[4] Outcomes of such reconstructive surgery are oftentimes less than adequate, however, and result in chronic physical and psychosocial sequelae for the patient.[5]

With the advent of vascularized composite allotransplantation (VCA), face and hand transplantation have emerged as attractive reconstructive options for survivors of major burns. The number of burn patients who are candidates for VCA is currently unknown due to variability in selection criteria between centers. Decision modeling analysis has also shown that if life expectancy after VCA is reduced due to the current obligatory requirement for lifelong immunosuppression after transplantation, the overall gain in quality-adjusted life years is similarly decreased.[6] However, this finding is in disconnect

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with individual psychological assessments of patients who have undergone VCA following burn injury.[7]

Nevertheless, the growing clinical experience in VCA has confirmed technical feasibility of burn reconstruction with face and hand allografts. Much debate has recently been generated with regard to minimizing pre-VCA sensitization events, desensitization techniques, patient selection, and improving access to VCA for burn patients.[8] The purpose of this study was to review all reported cases of VCA to date that have been performed for an underlying burn etiology, including the immunological considerations and events involved, when available.

METHODS

A literature review was performed using PubMed and lay media sources. All reported cases up to July 2016 were verified between publications and news reports (if necessary) before inclusion for analysis. Relevant data extracted included patient demographic profile, burn etiology (thermal, electrical, chemical), the type and extent of VCA performed, pretransplant panel reactive antibody (PRA) status, extent of human leukocyte antigen (HLA) mismatch between donor and recipient, and summary immunologic outcomes at the time of performance of this study (Table 1).

RESULTS

As of August 2015, a total of 110 upper extremity and 32 face transplants have been reported worldwide. Of these 142 known cases of VCA, 30 (21%) were performed for burn reconstruction with the majority of these cases occurring in the United States (n = 8) followed by France and Turkey (n = 5 each).

Patient Demographics

The majority of burn patients who had undergone VCA were male (n = 18, 86%), with an average age of 35.9 years (range, 19–59) at the time of surgery. These numbers did not differ significantly between the upper extremity and facial VCA subgroups (38.2 vs 33.4 years; $P = .34$). The time interval between the initial burn injury and VCA averaged 8.3 years (range, 1–23.5) and similarly was not significantly different between upper extremity and facial VCA patients (6.4 vs 10.5 years; $P = .25$). Incidentally, all VCA cases performed in Turkey were for reconstruction of burns suffered in childhood (range, 40 days to 13 years old). There have also been three reported deaths in this cohort of burns VCA patients, and all were recipients of combined VCA procedures (face, upper, or lower extremities; see "*Type and Extent of VCA Performed*").

Burn Etiology and Severity

Overall, the most common type of burns suffered was thermal (57%), followed by electrical burns (38%). Again, the proportion of thermal and electrical burns was similar in the upper extremity and facial VCA subgroups. There was only one case of chemical burns due to domestic violence, and this patient was reconstructed with a facial VCA.[9] The degree of burn injury was not uniformly reported, but third-degree burns involving 50 to >80% of the total BSA have been described.[9–11]

Type and Extent of Vascularized Composite Allotransplantation Performed

Of the 11 patients who had undergone upper extremity VCA, two were unilateral cases. The remaining nine patients underwent bilateral transplantation at different levels (hand/distal forearm, below elbow, above elbow), and three of them had simultaneous combined procedures (face, bilateral lower limb, unilateral lower limb). Of note, in all three combined VCA cases, there was 100% mortality at postoperative days (PODs) 4, 65, and 100 due to metabolic failure,[12] infection requiring allograft removal, complicated by on-table cardiac arrest,[11] and organ failure, respectively.[13] Retrospective analysis of the patient case that developed cardiac arrest suggested that infection and the resulting circulatory insult was due to an indolent and multidrug resistant strain of *Pseudomonas aeruginosa* identical to that isolated during his initial burn treatment[14]; detailed information about the other two cases have not been reported. Among the patients who received facial VCAs (cutaneous only, myocutaneous, and osteomyocutaneous), both partial (30%) and full facial allografts were transplanted.

Prevascularized Composite Allotransplantation Immunologic Status

Details of individual patient records were not uniformly available or reported. However, from the available data, pretransplant PRA ranged from 0 to 98%, and the extent of HLA mismatch between donors and recipients varied from 2/6 to 6/6. Prior possible sensitization events included more than 50 surgeries,[9] previous pregnancies, and multiple transfusions. All patients were matched for blood group and had negative pretransplant cross matches except for one (with chemical burns).[9]

Table 1. Overview of VCA performed for burn reconstruction

Patient/ Reference	Date of VCA	VCA Performed	Age/Sex of Patient	Team	Interval to VCA	Type of Burn	PRA Status	HLA Mismatch	Outcome
Face									
1[9]	Apr 09	Partial MC face + bilateral below elbow	37/M	France	1 yr	Thermal (self-harm)	Positive	4/6	VCA removal at POD 31, death on POD 65
2[10]	Apr 09	Partial OMC face	59/M	USA	4 yr	Electrical (accident)	?	3/6	Banff II and III (at POM 34, 56)
3[11]	Nov 09	Partial OMC face	27/M	France	1 yr	Thermal (pyrotechnic)	?	5/6	EBV lymphoma; acute rejection ×8; chronic rejection
4[12]	Mar 11	Full MC face	25/M	USA	3 yr	Electrical (accident)	68%	5/6	Banff III (at POM 22)
5[12]	Apr 11	Full MC face	30/M	USA	10 yr	Electrical (accident)	0%	2/6	Banff I–II (POD 20), II–III (POM 17)
6[13,14]	Jan 12	Full cutaneous face	19/M	Turkey	19 yr	Thermal (accident at 40 d old)	?	?	?
7[13,15]	Feb 12	Full cutaneous face	25/M	Turkey	23 yr	Thermal (accident at 2 yr old)	?	?	?
8[13,15]	May 12	Full cutaneous face	27/M	Turkey	23.5 yr	Thermal (accident at 3.5 yr old)	?	?	?
9[16]	Feb 13	Full MC face	44/F	USA	6 yr	Chemical (domestic)	98%	6/6	Banff III AMR (at POD 5)
10[17]	Aug 15	Full OMC face	41/M	USA	14 yr	Thermal (accident)	?	6/6	?
Upper extremity									
11[18]	Feb 03	Bilateral forearm	41/M	Austria	3 yr	Electrical	0%	4/6	Acute rejection ×8; AMR at 9 yr
12[19]	Feb 07	Bilateral hand	27/F	France	3 yr	Electrical	?	4/6	Banff II, II, III, II, III (at POD 16, 271, 635, 951, 1365)
13[19]	Jul 08	Bilateral hand	28/M	France	5 yr	Thermal	?	3/6	Banff II (POD 65)
14[20]	Nov 08	Bilateral above elbow	29/M	Spain	1 yr	Electrical	<20%	6/6	Banff III (at POM 6, 13, 26)
15[21]	Nov 08	Unilateral hand	43/M	USA	2 yr	Thermal	0%	?	Banff II ×4 (within 1st year post-VCA)
16[21]	Aug 10	Bilateral hand	55/M	USA	4 yr	Thermal	0%	?	Banff II ×2 (by POD 86); AMR at POM 6; chronic rejection
17[22]	Jan 12	Bilateral arm + single lower limb	34/M	Turkey	23 yr	Electrical (accident at 11 yr old)	?	?	Lower limb lost on POD 1, death ~ POD 100
18[23]	Feb 12	Bilateral above elbow + bilateral lower limb	27/M	Turkey	14 yr	Electrical (accident at 13 yr old)	?	6/6	Death on POD 4
19[24]	Oct 12	Unilateral hand	44/M	USA	9 yr	Thermal	0%	4/6	No acute rejection to date
20[25]	Mar 14	Bilateral hand	55/M	Austria	5 yr	Thermal	0%	6/6	Banff I–II (POD 112)

AMR, antibody-mediated rejection; *EBV*, Epstein-Barr virus; *F*, female; *HLA*, human leukocyte antigen; *M*, male; *MC*, myocutaneous; *OMC*, osteomyocutaneous; *POD*, postoperative day; *POM*, postoperative month; *PRA*, panel reactive antibody; *VCA*, vascularized composite allotransplantation.

Immunological Outcomes

Besides a fingertip amputation and chronic rejection of a hand allograft requiring amputation due to severe ischemia,[15] no other allograft loss has been reported in the group of surviving patients, but they have experienced an average of three (range, 0–8) acute skin rejection episodes from as early as POD 5 to first occurrence at 36 months post-VCA, with corresponding histological grades ranging from Banff I to III. While the majority of acute rejection episodes in VCA were treated successfully with steroid pulses and/or by increasing the dose of calcineurin inhibitors,[16] this cohort of VCA burn patients has seen the introduction of various adjuncts including topical tacrolimus,[17] basiliximab and alemtuzumab,[18,19] and rituximab[18] for the treatment of steroid and antithymocyte globulin (ATG) refractory acute rejection. Of note, only one living VCA recipient (upper extremity) has been reported to remain rejection free at 3 years posttransplantation,[10] in contrast to the majority who developed acute rejection within the first year.[16]

Antibody-mediated rejection (AMR) was reported in three patients both early (POD 5 after facial VCA)[9] and late (at 6 months[15] and 9 years[18] after upper extremity VCA); one of these cases also occurred in the absence of donor-specific antibodies (DSA; but became DSA positive two days after allograft removal).[15] One patient, who is currently 6 years status after facial VCA, developed Epstein-Barr virus lymphoma, likely due to chronic immunosuppression. Titration of overall immunosuppression as part of the lymphoma treatment has since led to multiple acute rejection episodes that, although adequately treated, have now culminated with the recent development of features suggestive of chronic rejection in VCA.[20]

While the majority of VCA recipients are maintained on conventional triple immunosuppression consisting of tacrolimus, mycophenolate mofetil, and methylprednisolone,[16] various regimen modifications have been reported in order to reduce the overall burden of immunosuppression and associated complications as described earlier. In an effort to induce tolerance, bone marrow cell infusion was performed on POD 4 in one facial VCA recipient (without preparatory conditioning), but this was unsuccessful and he remains on immunosuppression.[20] Other groups have attempted withdrawal of maintenance steroids from 2 to 12 months post-VCA[17,21], but acute rejection episodes persisted and required increasing tacrolimus and mycophenolate mofetil dosages as well as steroid boluses with subsequent taper, and even ATG for resolution.[22] Various other modifications to maintenance regimens have also been reported in this group of VCA burn patients such as the introduction of sirolimus and the substitution of tacrolimus with everolimus.[18,20]

In one patient with preformed DSA, induction therapy required additional plasmapheresis and intravenous immunoglobulin treatment every other day from POD 1 onward; following the development of antibody-mediated acute rejection on POD 5, rescue therapy required further plasmapheresis, intravenous immunoglobulin, ATG, steroid bolus, and additional eculizumab, bortezomib, and alemtuzumab.[9] This observation led us to compare the induction and treatment regimens between sensitized (defined as PRA > 0 in this study) and nonsensitized (PRA = 0%) VCA patients (Table 2). Patients who were sensitized pre-VCA had various adjuncts (eg, extracorporeal photopharesis, plasmapharesis) in addition to standard induction with T-cell depletion and, in contrast to nonsensitized patients, were still more likely to have preformed DSA or produce DSA subsequent to transplantation. Interestingly, one of the nonsensitized, upper extremity VCA patients had erythrocyte concentrate (the origin of which was not reported) given as part of induction and eventually became "sensitized," developing DSA and consequent AMR, 9 years later.[18] While donor-specific transfusions have previously been shown to have an immunomodulatory effect in renal transplantation,[23] this particular patient developed three episodes of steroid- and ATG-resistant acute rejection within the first 6 months and required rescue therapy with alemtuzumab.[24] Further observation suggests that current, triple immunosuppression regimens will most likely be required for long-term maintenance to prevent or minimize rejection episodes. This conclusion is based on the fact that, ultimately, most patients who were on steroid-sparing protocols, had to be treated with additional steroids when rejection developed and some also required reintroduction of steroids for maintenance (Table 2).

Opportunistic infections due to chronic immunosuppression have also been reported. In recipients who were serology negative for cytomegalovirus but received allografts from donors who were positive, cytomegalovirus infections developed from POD 210[17] up to POD 460.[21] Epstein-Barr virus infection has also been reported at POD 603[25] and has led to lymphoma as described previously.[20]

Finally, although not a focus of this review, functional and psychosocial outcomes have been reported elsewhere.[26]

Table 2. Comparison of treatment of rejection episodes between sensitized and nonsensitized VCA burn patients

Patient/ Reference	VCA	Induction	Maintenance Immunosuppression	Acute Rejection	DSA	Rescue Therapy
Sensitized						
1[9]	Face	ATG, ECP	FK506, MMF, prednisone	No	Yes	—
4[12]	Face	ATG, methylprednisolone	FK506, MMF, prednisone (steroid withdrawal at POM 2)	Yes (POM 22)	No	FK506 adjustment + ointment, ATG dexamethasone rinse, steroid bolus and taper
9[16]	Face	ATG, IVIG, methylprednisolone, plasmapheresis	FK506, MMF, prednisone (steroid withdrawal at POM 2)	Yes (POD 5)	Yes (pre-VCA)	Steroid bolus, ATG, IVIG, plasmapheresis, eculizumab, bortezomib, alemtuzumab
14[20]	Upper extremity	Alemtuzumab, methylprednisolone	FK506 (switched to sirolimus on POD 332), MMF, prednisone (introduced after POM 6)	Yes (POM 6)	Yes	Steroid bolus and taper to maintenance
Nonsensitized						
5[12]	Face	ATG	FK506, MMF, prednisone (steroid withdrawal at POM 2)	Yes (POD 20, POM 17)	No	FK506 and MMF adjustment, steroid bolus; FK506 and MMF adjustment, steroid bolus and taper
11[18]	Upper extremity	ATG, erythrocyte concentrate	FK506, MMF, prednisone (steroid withdrawal from years 3–5), everolimus (introduced with gradual FK506 reduction)	Yes (6 in first 3 years)	Yes (year 9)	IV and topical steroids, FK506 adjustment, basiliximab, ATG, alemtuzumab; rituximab for year 9 AMR
15[21]	Upper extremity	Alemtuzumab	FK506, MMF (introduced after POM 1; converted to sirolimus from POM 6 due to GV), prednisone (introduced POM 6)	Yes (POM 1)	No	FK506 adjustment, MMF
16[21]	Upper extremity	Alemtuzumab	FK506, MMF (converted to sirolimus from POM 6 due to GV), prednisone	Yes (×2 by POD 86)	No	— (But developed GV requiring IVIG and plasmapheresis)
19[24]	Upper extremity	ATG		FK506, MMF, prednisone	No	No
20[25]	Upper extremity	Alemtuzumab	FK506, MMF, prednisone (withdrawn from POD 21), belatacept (started on POD 100 due to renal insufficiency)	Yes (POD 112)	No	IV steroid bolus ×3

ATG, antithymocyte globulin; *DSA*, donor-specific antibodies; *ECP*, extracorporeal photopharesis; *FK506*, tacrolimus; *GV*, graft vasculopathy; *IVIG*, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *POM*, postoperative month; *VCA*, vascularized composite allotransplantation.

DISCUSSION

It is clear from this review that reconstructive transplantation of the upper extremity and craniofacial region can be successfully performed in burn patients for whom no other suitable treatment options exist to improve their quality of life.

At present, most VCA centers follow selection criteria that have been well established in solid organ transplantation,[27] including ABO compatibility and negative pretransplant crossmatch. However, difficulty in finding matching donors with similar color and size of allografts translates to VCA being performed between donor–recipient transplant pairs with varying degrees of HLA mismatch, ranging from 2/6 to 6/6 in the current study. Although data suggest that the extent of HLA matching improves transplant outcomes in solid organ transplantation,[26] in this cohort of burn patients who have undergone VCA, the immediate outcomes of patient and allograft survival and the incidence of acute rejection do not seem to correlate with HLA matching (eg, patient 4 had a HLA mismatch of 5/6 but only developed the first episode of rejection 22 months posttransplantation, whereas in patient 5, despite a more "favorable" HLA mismatch at 2/6, he developed rejection by POD 20). A possible confounding factor is the potential for discrepancy between clinical presentation and histological diagnosis of acute rejection based on the current Banff VCA working classification, especially for grade I episodes that are considered "mild."[28] Although histology is the current accepted standard for diagnosis, there remains much interobserver variation in assessment outcomes based on the current Banff grading system.[29] Consequently, treatment dilemmas arise in the event of subclinical rejection, especially when diagnosed through surveillance rather than "for-cause" biopsies. Moreover, the necessity for treating both subclinical and mild–moderate (Banff I–II) rejection episodes remain equivocal and its long-term immunological impact is still poorly understood. Regardless, clinical correlation with histology is paramount and follow-up biopsies to document histological resolution following treatment of rejection is usually performed at most VCA centers.[28] It is clear that, despite initial enthusiasm for the "ease" of monitoring VCAs by visual inspection, these diagnostic and therapeutic challenges have led to ongoing investigations on various combinations of monitoring modalities[30] including sentinel allo-skin grafts (from the same VCA donor), additional protocol biopsies for random surveillance, Duplex ultrasound, MRI, and even novel technologies such as ultrasound biomicroscopy.[15] Therefore, with the concurrent, growing clinical experience in VCA, the Banff VCA classification will continue to evolve and undergo refinement to improve its diagnostic sensitivity and specificity. Until then, the impact of the different extent of HLA mismatches on VCA rejection remains to be determined.

Much debate has been generated with regard to the allocation of resources to highly sensitized burn patients who may be candidates for VCA.[8] However, it appears that immunologic issues related to anti-HLA sensitization are not a major limitation in performing VCA in such patients. In the French experience, an electrical burn survivor was removed from the transplant waiting list for facial VCA after 18 months because of persistently high PRA levels and positive crossmatches with all potential donors; this patient had received prior skin allografts during acute burn care.[11,31] In contrast, a burn patient who had been on the wait-list for 14 months in the United States underwent VCA despite a PRA of 98%, a positive crossmatch, and a preexisting DSA to the identified donor.[9] In view of the differing experiences, it has been suggested that surgeons and physicians review the acute management of severe burn injuries with regard to the multitude of possible sensitization events, such as the use of cadaveric allograft skin for temporary wound coverage, multiple blood transfusions, and support devices such as extracorporal membrane oxygenation and renal dialysis.[32] Immunologically, the introduction of foreign antigens naturally (via pregnancy) and iatrogenically (eg, blood transfusions, allogeneic skin grafting, extracorporal membrane oxygenation) is probably unavoidable and it would not be realistic to withhold or compromise life-supporting treatment during acute burn care because the patient may, potentially, become a candidate for VCA some 5 to 10 years later. A recent study by Win et al[31] has shown that in major burns patients with an average TBSA of 47.5 ± 13%, treatment with blood transfusions (average, 21.7 ± 17.3 units) and cadaveric skin allografts (from an average of 5.25 ± 4.1 deceased donors) resulted in a PRA of 87.7 ± 27.6% at approximately 4.36 ± 2.06 years following burn injury. Similarly, Duhamel et al[33] showed that the treatment of 54 ± 11% of TBSA burns required an average of 36 ± 13 units of packed red blood cells (PRBCs) for transfusion with 62% of patients developing a resulting PRA of ≥85% (ie, highly sensitized, to be excluded from transplantation) at approximately 3 ± 1 years later. It should be noted that a high pretransplant PRA is associated with a higher risk of *developing* DSA subsequently and does not necessarily equate to the preexistence of DSA. However, one can certainly have both, as

seen in the patient with chemical burns in this series, who subsequently developed even higher levels of the preexisting DSAs, which, not surprisingly, resulted in acute AMR by POD 5.[9] By extension, one would presume that the development of new, *de novo* DSA and/or increase in pretransplant DSA after transplantation would correlate with increasing severity of immunological outcomes, but threshold levels based on mean fluorescent intensity have not been shown to be predictive. Rather, the likelihood of treatment success cannot be defined or measured simply by resolution of mean fluorescent intensity because DSA are rarely, if ever, removed.[34]

While desensitization can certainly be attempted, perhaps it would be more worthwhile to recognize the potential deleterious role of memory T-cells in these sensitization events and transplantation[35] and to devise therapeutic strategies to overcome the challenges posed. For instance, the use of glycerol-preserved skin grafts has been purported to stimulate less of an antigenic response compared with cryopreserved skin grafts[33] but this change alone will certainly not be adequate in mitigating the risks of sensitization in acute burn care. Moreover, in the actual VCA procedure itself, blood product requirements are highly variable and may range from just two units of PRBCs[17] to 66 units of PRBCs and an additional 9 and 62 units of platelets and fresh frozen plasma.[11] Perhaps most importantly, memory T-cells are resistant to both depletional[36] and costimulatory blockade[37] strategies and portend a highly formidable immunological barrier in VCA.

Yet, preclinical, large animal studies in nonhuman primates have suggested that the high, pretransplant frequencies of memory T-cells may not be insurmountable when ATG is administered in combination with tocilizumab, a monoclonal antibody against IL-6 receptor, as part of induction therapy in lung transplantation.[38] Subsequently, with standard triple immunosuppression maintenance, rejection- and DSA-free allograft survival of >100 days was achieved and attributed to the in vivo upregulation of regulatory T-cells resulting from this protocol.[39] More recently, a similar approach has been reported clinically in small intestinal transplantation, whereby the in vivo upregulation of regulatory T-cells could avoid sensitization, ameliorate acute rejection, and enable prolongation of allograft survival.[40] Donor blood transfusion, the avoidance of high-dose immunosuppression, minimization of ischemia-reperfusion injury in the allograft, and the selection of infection-free donors were key components to the success of this protocol. In turn, fulfillment of these conditions contributed toward an inflammation-contained environment that presumably enabled proliferation of regulatory T-cells with immunosuppressive functions and a decrease in the numbers of effector-type memory T-cells. Application of such immunomodulatory protocols to burn patients undergoing VCA may therefore be more realistic and of greater utility.

The success of burn care is determined by the extent of social reintegration that can be achieved by the burn survivor. VCA offers an ideal treatment for patients recovering from major burns but at the same time represents an immunological challenge with far-reaching and potentially lethal consequences. Further development and refinement of clinically relevant immunomodulatory protocols are required to achieve immunosuppression–minimization and/or successful transplantation tolerance to enable long-term survival of both the VCA and the patient.

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