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MECHANISMS OF REJECTIONS AND TOLERANCE STRATEGIES IN VASCULARIZED COMPOSITE ALLOTRANSPLANTATION: A COMPREHENSIVE REVIEW

Benedetto Longo, Angelica Pistoia, Gennaro D'Orsi, Valerio Cervelli

Chair of Plastic Surgery, Department of Surgical Sciences, University of Rome Tor Vergata, Rome, Italy

Summary

Vascularized composite allotransplantation (VCA) offers unique reconstructive potential, yet long-term success remains constrained by immune rejection. Acute rejection, driven by T-cell activation following ischemia–reperfusion injury and dendritic-cell priming, is common during the first postoperative year. Concurrent B-cell activation and donor-specific antibody (DSA) formation contribute to antibody-mediated rejection (AMR) and increase the risk of progression toward chronic injury. Chronic rejection is characterized by graft vasculopathy, with endothelial activation, intimal hyperplasia, and gradual luminal narrowing, leading to graft dysfunction.

Patients with burns, transfusions, or temporary skin allografts often have pre-existing sensitization, which increases susceptibility to early AMR and the development of new DSA. In addition, activation of the innate immune system by damage-associated molecules (DAMPs) and pro-inflammatory cytokines further enhances adaptive immune responses, resulting in an environment that is highly prone to rejection.

Emerging tolerance-focused strategies aim to lessen lifelong immunosuppression requirements. Approaches such as mixed hematopoietic chimerism, regulatory T-cell (Treg) and mesenchymal stromal cell (MSC) therapies, as well as decellularization/recellularization techniques and machine perfusion, seek to improve graft compatibility and maintain structure.

In this review, we aim to synthesize current evidence on the immunological mechanisms underlying acute and chronic rejection, pathways of sensitization, and emerging strategies designed to reduce immunogenicity and promote long-term tolerance in VCA.

Key words: vascularized composite allotransplantation (VCA), decellularization, rejection, donor-specific-antibody (DSA), transplant

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Correspondence
Benedetto Longo
E-mail: benedetto.longo@uniroma2.it

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INTRODUCTION

Vascularized composite allotransplantation (VCA) has revolutionized reconstructive microsurgery [1,2], allowing restoration of both form and function

after devastating tissue loss [3-5]. Since the first successful hand transplant in 1998, more than two hundred VCAs, including hand, face [6], and abdominal wall transplants, have been performed worldwide [7], with encouraging functional and psychological outcomes [8-10]. However, the major limitation to long-term success remains immune rejection [11].

Acute rejection is highly prevalent after VCA and remains the most common early complication, while chronic rejection continues to limit long-term graft survival [12]. It is primarily T cell-mediated, driven by direct and indirect antigen presentation pathways, and manifests clinically with erythema, edema, and epidermal necrosis [13]. Because of its high immunogenicity, the skin is the primary clinical target of rejection in VCA [14]. Although most acute episodes can be reversed with intensified immunosuppression, chronic rejection, dominated by graft vasculopathy (GV), remains a critical unresolved challenge [15]. GV, reported in approximately 6% of clinical VCA cases, is characterized by endothelial injury, concentric intimal hyperplasia, and progressive luminal narrowing [16]. The frequent association of donor-specific antibodies (DSA) and C4d deposition highlights the role of antibody-mediated rejection (AMR) in chronic graft loss [17,18].

The immunologic landscape of VCA is unique, combining highly antigenic (skin and mucosa) and potentially tolerogenic (vascularized bone marrow and muscle) tissues within the same graft [19]. Many recipients are pre-sensitized through prior transfusions, burns, or skin grafts, predisposing them to early antibody formation and immune activation [20]. Consequently, there is increasing interest in developing immunological tolerance strategies to achieve long-term graft survival with reduced or discontinued systemic immunosuppression [21]. Promising experimental and translational approaches include mixed hematopoietic chimerism, which promotes central deletion of alloreactive clones and peripheral expansion of regulatory T cells (Tregs) [22,23]. In parallel, cell-based immunotherapy using Tregs or mesenchymal stromal cells (MSCs) has been shown to suppress alloreactivity, modulate dendritic cell function, and enhance tissue repair [23,24]. Furthermore, decellularization and recellularization technologies are being explored to minimize graft immunogenicity while preserving structural and vascular integrity [25].

Despite these advances, the mechanisms underlying acute and chronic rejection, sensitization, and tolerance induction in VCA remain incompletely understood. This manuscript is a narrative review that synthesizes current knowledge on immune rejection, sensitization, and tolerance strategies in vascularized composite allotransplantation (VCA). A focused literature search was conducted using PubMed/MEDLINE and Scopus, covering articles published up to December 2025. Search terms included “vascularized composite allotransplantation”, “acute rejection”, “antibody-mediated rejection”, “chronic rejection”, “graft vasculopathy”, “sensitization”, “donor-specific antibodies”, “tolerance”, “chimerism”, “regulatory T cells”, and “bioengineering”. Priority was given to clinical studies of human VCA, while preclinical VCA models and evidence extrapolated from solid-organ transplantation were included when they provided relevant mechanistic or translational insights applicable to composite allografts.

The purpose of this review is therefore to summarize the current clinical evidence on the immunological mechanisms of rejection and tolerance, focusing on acute and chronic processes, pathways of sensitization, and emerging strategies that may enable durable graft survival with minimal immunosuppression (Fig. 1).

MECHANISMS OF ACUTE AND CHRONIC REJECTION

The immunopathophysiology of rejection in vascularized composite allotransplantation (VCA) reflects a complex interplay between innate and adaptive immune responses.

Acute rejection is primarily T cell-mediated and represents the most common complication after VCA, occurring in more than 85% of recipients during the first postoperative year [12,26]. Clinically, it typically presents with skin erythema, edema, rash, or epidermal changes, reflecting the high immunogenicity of the cutaneous component. The process is initiated immediately following reperfusion, when ischemia–reperfusion injury triggers the release of damage-associated molecular patterns (DAMPs) that activate innate immune cells through toll-like and pattern-recognition receptors [27]. Activated dendritic cells (DCs) migrate to regional lymph nodes, where they present alloantigen to naïve $CD4^+$ and $CD8^+$ T lymphocytes, initiating clonal expansion and differentiation into effector cells [28].

The effector phase is driven by cytotoxic $CD8^+$ T cells and Th1/Th17 $CD4^+$ subsets, which infiltrate graft tissue and release inflammatory cytokines such as interleukin (IL)-2, interferon-γ, IL-6, and tumor necrosis factor-α, leading to endothelial activation, keratinocyte apoptosis, and microvascular injury [29]. Histologically, acute cellular rejection is characterized by dense perivascular mononuclear infiltrates, epidermal interface damage, and adnexal involvement, graded according to the Banff classification [30]. The skin, rich in antigen-presenting Langerhans cells and highly vascularized, remains the dominant target and clinical indicator of rejection [31]. In parallel, humoral immune activation contributes to

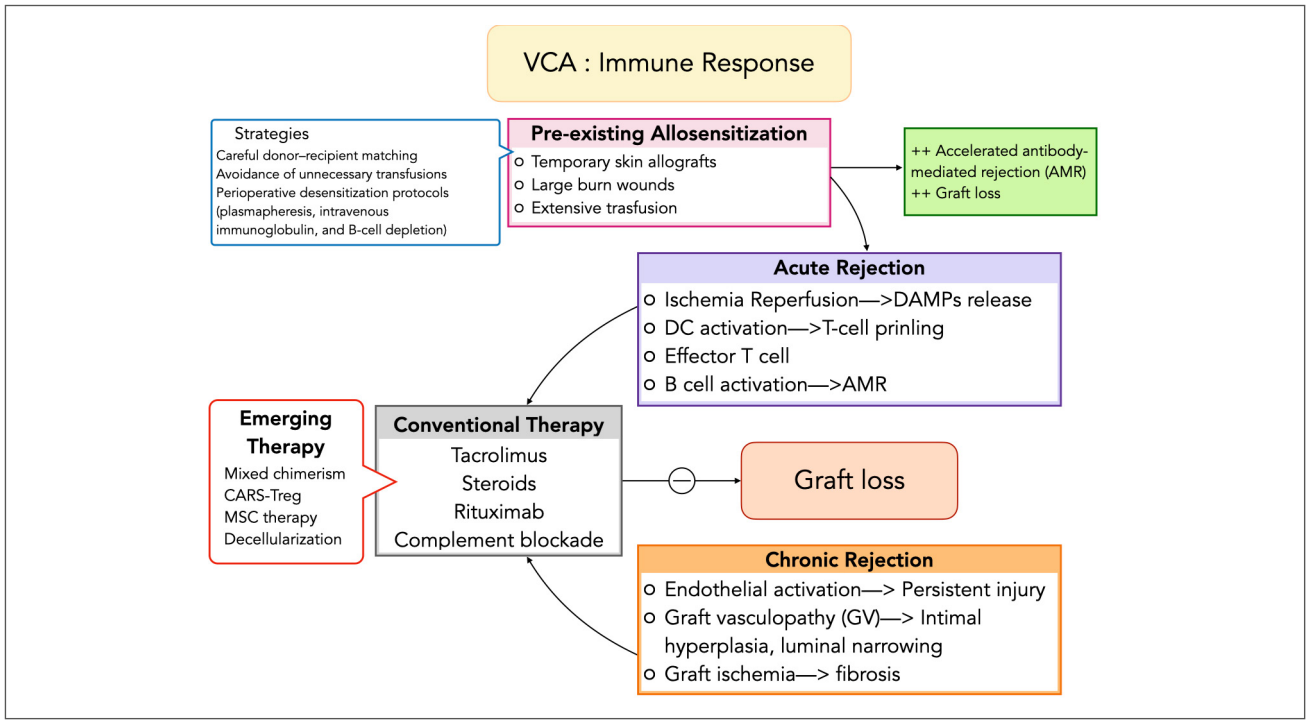


Figure 1. Diagram illustrating sensitization pathways and immune rejection mechanisms in vascularized composite allotransplantation (VCA), together with current standard therapies and emerging tolerance-oriented approaches. In cases of pre-sensitization, the risk of acute rejection is increased or accelerated. AMR: antibody-mediated rejection; DSA: donor-specific antibodies; MSC: mesenchymal stromal cell; DAMPs: damage-associated molecular patterns; DC: dendritic-cell; CARs: chimeric antigen receptors.

graft injury through antibody-mediated rejection (AMR). B-cell activation, often facilitated by T-follicular helper cells, results in the production of donor-specific antibodies (DSA) directed against HLA class I and II antigens [32]. These antibodies bind to the vascular endothelium, fix complement, and induce C4d deposition, promoting endothelial activation, microthrombosis, and tissue ischemia [18]. The coexistence of DSA and cellular rejection episodes increases the risk of progression to chronic vasculopathy. In clinical VCA, AMR may occur either early – particularly in presensitized recipients – or late, often after reduction of immunosuppression [33]. In VCA, antibody-mediated rejection may present with microvascular injury, edema, and graft dysfunction and is supported diagnostically by the detection of circulating donor-specific antibodies, evidence of complement activation including C4d deposition, and histologic signs of endothelial damage or capillaritis.

Chronic rejection represents the long-term, cumulative manifestation of immune injury and is characterized by graft vasculopathy (GV), leading to ischemia, fibrosis, and graft dysfunction [15]. The pathologic hallmark is concentric myointimal hyperplasia resulting from chronic endothelial activation, smooth-muscle cell proliferation, and extracellular matrix deposition [34]. GV affects medium and small arteries of the graft and is associated with luminal narrowing, ischemia, and secondary fibrosis of skin and subcutaneous tissues. Although the reported clinical incidence of GV in VCA is relatively low (≈ 6%), its impact is severe, frequently culminating in graft loss or amputation [35].

The mechanisms driving GV are multifactorial, involving both cellular rejection – sustained infiltration of T cells and macrophages – and humoral responses, particularly persistent or recurrent DSAs [36]. Non-immunologic contributors, such as endothelial dysfunction, hyperlipidemia, and prothrombotic states, further accelerate vascular remodeling. Experimental studies have demonstrated that chronic endothelial activation leads to overexpression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and increased smooth muscle migration, whereas macrophage-derived cytokines such as TGF-β and PDGF promote fibrointimal proliferation [37].

Altogether, acute and chronic rejection represent a continuous spectrum of immune-mediated graft injury. Acute T-cell-driven inflammation provides the initial insult, while antibody-mediated and vascular remodeling mechanisms perpetuate chronic changes. This continuum underscores the necessity of combined cellular and humoral control in VCA, as well as the potential of

Table I. Key distinguishing features of acute cellular rejection, antibody-mediated rejection, and chronic rejection (graft vasculopathy) in vascularized composite allotransplantation, including typical timing, primary immune mechanisms, diagnostic criteria, and clinical implications.

Feature	Acute cellular rejection (ACR)	Antibody-mediated rejection (AMR)	Chronic rejection/graft vasculopathy (GV)
Primary immune mechanism	T cell-mediated	Antibody-mediated (DSA)	Mixed cellular and humoral
Typical timing	Early (weeks-months; common in first year)	Early or late	Late (months-years)
Main target	Skin and microvasculature	Endothelium	Medium and small vessels
Clinical presentation	Skin erythema, edema, rash, epidermal changes	Edema, graft dysfunction, microvascular injury	Progressive ischemia, fibrosis, functional decline
Histopathologic features	Perivascular mononuclear infiltrates, epidermal interface changes, adnexal involvement	Endothelial injury, capillaritis, microthrombosis	Concentric intimal hyperplasia, luminal narrowing
Immunologic markers	Activated T cells	Donor-specific antibodies (HLA I/II)	Persistent or recurrent donor-specific antibodies
Complement involvement	No	Yes (C4d deposition)	Variable
Diagnostic framework	Clinical signs plus Banff histologic grading	Donor-specific antibodies plus histology with or without C4d	Histopathology with or without immunologic markers
Reversibility	Usually reversible	Variable	Often irreversible

tolerance-inducing approaches – such as regulatory T-cell therapy, mixed chimerism, and immunomodulatory stem cell strategies – to interrupt this progression and achieve long-term graft survival [38].

The main clinical and pathological features of ACR, AMR, and chronic graft vasculopathy in VCA are summarized in Table I.

MECHANISMS OF IMMUNE SENSITIZATION

In the context of vascularized composite allotransplantation, sensitization is operationally defined by the presence of preformed donor-specific antibodies, elevated calculated panel reactive antibody values, and/or a positive donor-recipient crossmatch. Sensitization has direct implications for candidate selection, donor matching, perioperative desensitization strategies, and post-transplant immunologic monitoring. Sensitized recipients are at increased risk of early antibody-mediated rejection and de novo donor-specific antibody formation, necessitating individualized immunosuppressive and desensitization protocols. Immune sensitization is a major determinant of graft outcome in vascularized composite allotransplantation (VCA). Unlike in solid organ transplantation (SOT), many VCA candidates present with pre-existing allosensitization due to extensive transfusions, temporary skin allografts, or the inflammatory milieu of large burn wounds. These factors promote the generation of preformed anti-HLA antibodies, complicating donor selection and increasing the risk of early antibody-mediated rejection (AMR) and graft loss [20]. In clinical series, sensitized recipients display higher rates of acute rejection and de novo donor-specific antibody (DSA) formation, even under intensified immunosuppression [33].

The mechanisms of sensitization involve both humoral and cellular immune activation. Alloantigen exposure induces B-cell proliferation and differentiation into long-lived plasma cells, resulting in the production of high-affinity anti-HLA and non-HLA antibodies. Non-HLA reactivities – such as those targeting angiotensin II type-1 receptor or vimentin – have been detected in patients with recurrent rejection or chronic vasculopathy [39]. These antibodies can activate endothelium independently of complement, promoting inflammation and thrombosis. At the same time, memory T cells, previously primed through infections or environmental cross-reactivity, recognize allogeneic peptides and mount rapid effector responses upon re-exposure [40]. The coexistence of these two immune memory pathways – humoral and cellular – creates a state of heightened immunologic readiness that is difficult to control with conventional therapy.

Preformed DSAs can bind to graft endothelium at reperfusion, triggering hyperacute or accelerated AMR. Complement activation leads to C4d deposition, platelet aggregation, and microvascular injury. This phenomenon, although rare, has been documented in presensitized face transplant recipients with positive crossmatches, necessitating early plasmapheresis,

rituximab, or complement blockade to achieve partial reversal [41,42]. More commonly, secondary sensitization occurs post-transplant due to subclinical antigen exposure or insufficient immunosuppression. These de novo DSAs often appear after episodes of cellular rejection, supporting the concept that T-cell activation facilitates B-cell alloimmunity [43].

Innate immune activation amplifies sensitization. Ischemia-reperfusion injury (IRI) during transplantation releases damage-associated molecular patterns (DAMPs) that activate macrophages and dendritic cells via toll-like receptors, bridging the innate and adaptive arms of immunity. Cytokines such as IL-1β, IL-6, and TNF-α enhance antigen presentation and costimulation, thereby promoting the differentiation of effector T and B cells. Experimental evidence indicates that even transient innate activation can significantly amplify alloantibody responses and accelerate graft vasculopathy [28].

From a clinical perspective, strategies to mitigate sensitization include careful donor-recipient matching, avoidance of unnecessary transfusions, and perioperative desensitization protocols employing plasmapheresis, intravenous immunoglobulin, and B-cell depletion [20]. However, durable immunological control will likely require tolerance-inducing approaches that actively reprogram the immune system rather than suppress it. In this regard, the combination of mixed hematopoietic chimerism, regulatory T cells (Tregs), and costimulation blockade represents a rational path forward, providing both central and peripheral immune regulation and offering a potential solution to the challenges posed by pre-existing sensitization [44,45].

IMMUNOLOGICAL TOLERANCE AND CHIMERISM

Tolerance-inducing approaches in VCA are based on heterogeneous levels of evidence. Throughout this section, we explicitly distinguish between findings supported by clinical data in human VCA, those derived from preclinical VCA animal models, and strategies extrapolated from solid organ transplantation, to provide a balanced, translationally appropriate interpretation of current knowledge. The induction of immunological tolerance remains the ultimate goal in transplantation and represents the most promising path toward long-term graft survival without continuous pharmacologic immunosuppression. In vascularized composite allotransplantation (VCA), tolerance is particularly challenging due to the graft's antigenic diversity, which includes highly immunogenic components such as skin and mucosa alongside potentially tolerogenic structures, such as vascularized bone marrow (VBM) [19].

Chimerism, defined as the coexistence of donor and recipient hematopoietic lineages within a single immune system, offers a mechanistic basis for transplantation tolerance. Experimental models have shown that mixed hematopoietic chimerism – rather than full donor replacement – achieves immune tolerance by deleting donor-reactive T-cell clones in the thymus (central tolerance) and sustaining regulatory pathways in the periphery (peripheral tolerance) [46]. In VCA, the inclusion of VBM within osteomyocutaneous flaps facilitates spontaneous donor cell engraftment, resulting in transient multilineage chimerism detectable in blood and lymphoid organs [10]. Although this chimerism often wanes over time, even temporary coexistence has been associated with reduced rejection frequency and diminished allospecific T-cell responses in animal models [47].

Clinical experience from solid organ transplantation supports the translational potential of chimerism. In combined kidney-bone marrow transplantation, protocols employing non-myeloablative conditioning with total lymphoid irradiation and donor marrow infusion have achieved long-term graft survival with partial or complete withdrawal of immunosuppression in selected recipients. These results demonstrate that stable mixed chimerism can induce durable donor-specific tolerance without graft-versus-host disease (GvHD) [26]. However, such regimens remain limited in VCA due to procedural complexity, cytotoxic conditioning, and ethical concerns surrounding a non-life-saving procedure [48,49].

Regulatory T cells (Tregs) constitute a complementary and potentially safer approach to tolerance induction. Tregs maintain peripheral immune homeostasis by suppressing effector T-cell activation through cell contact, cytokine secretion (IL-10, TGF-β, IL-35), and checkpoint molecules (CTLA-4, PD-1) [50]. Experimental VCA studies have shown that the adoptive transfer of donor-specific or polyclonal Tregs prolongs graft survival and mitigates rejection without global immunosuppression. Human trials in solid organ transplantation, such as the ONE Study [51] and TASK trials [52], have confirmed the safety and partial efficacy of Treg therapy, allowing calcineurin inhibitor tapering and reduced infectious complications [49]. These findings suggest that Treg-based interventions could be feasibly integrated into VCA protocols, either as prophylaxis or as treatment for early rejection episodes [53].

Emerging work has expanded Treg-based strategies through genetic engineering. Chimeric antigen receptor (CAR)-modified Tregs and TCR-redirected Tregs have demonstrated targeted suppression of alloreactive responses in preclinical skin and heart transplant models [54]. These "living drugs" offer high antigen specificity and

sustained regulatory capacity, potentially combining with mixed chimerism or costimulation blockade to achieve donor-specific tolerance with minimal systemic toxicity [55].
Beyond hematopoietic and cellular strategies, mesenchymal stromal cells (MSCs) exhibit potent immunomodulatory and pro-regenerative properties that complement tolerance induction [56]. MSCs inhibit dendritic cell maturation, promote Treg expansion, and secrete anti-inflammatory mediators such as indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 [57]. In experimental VCA, MSC infusion has reduced acute rejection scores and preserved microvascular integrity [58].
The integration of these strategies, chimerism, Treg therapy, and MSC-based modulation, defines the next frontier of immune tolerance in VCA. Each target distinct yet converging pathways: central deletion via chimerism, peripheral regulation via Tregs, and microenvironmental stabilization via MSCs. Their combined use may enable a paradigm shift from immunosuppression-dependent maintenance to biologically sustained tolerance, reconciling durable graft acceptance with minimal systemic toxicity.
Despite their strong experimental rationale, tolerance-oriented strategies face significant barriers to clinical translation in VCA. These include the complexity of conditioning regimens, the potential toxicity of lymphodepletion or irradiation, ethical concerns related to non-life-saving transplantation, and uncertainties regarding the durability and reproducibility of tolerance. Furthermore, the immunologic heterogeneity of composite grafts and the frequent presence of pre-existing sensitization in VCA candidates complicate the application of protocols developed in solid organ transplantation. Consequently, these approaches should currently be regarded as promising but investigational, requiring careful clinical validation.

DECELLULARIZATION, BIOENGINEERING AND FUTURE PERSPECTIVES

Recent advances in tissue engineering and regenerative medicine have opened new frontiers for achieving immunologic tolerance in vascularized composite allotransplantation (VCA). Among these, decellularization and recellularization technologies aim to reduce graft antigenicity while preserving the extracellular matrix (ECM) architecture, vascular integrity, and biomechanical strength [59]. The concept is to remove all cellular and nuclear material – major sources of alloantigens – through chemical or physical processing, thereby creating an acellular scaffold that can be recellularized with the recipient's autologous cells [60]. Such grafts, by recapitulating donor structure without immunogenic cells, may obviate or drastically reduce the need for lifelong immunosuppression.
In experimental VCA, perfusion-based decellularization techniques using detergents such as sodium dodecyl sulfate (SDS) or Triton X-100 have successfully generated acellular limb or facial scaffolds with preserved vascular trees [61]. When these scaffolds are recellularized with recipient endothelial or mesenchymal cells, perfusion and microvascular patency can be restored, demonstrating the feasibility of "personalized" graft reconstruction [62,63]. Studies have shown that autologous recellularization can attenuate immune activation, promote angiogenesis, and support neural regeneration – critical elements for functional restoration in composite tissues [64,65].
Machine perfusion has further enhanced graft preservation and immune modulation. Normothermic and hypothermic perfusion systems maintain tissue viability ex vivo, extending preservation times while allowing active conditioning with oxygen, nutrients, or even immunoregulatory agents [66]. For example, perfusion with anti-inflammatory cytokines or stem-cell–derived extracellular vesicles can downregulate endothelial activation and reduce ischemia-reperfusion injury, which is a key amplifier of alloimmune priming [67,68]. The combination of machine perfusion and decellularized scaffolds may thus represent the next step toward "immunologically neutral" composite grafts suitable for delayed, customized implantation [5].
From an immunologic standpoint, these bioengineering advances align with the broader concept of immune minimization through graft modification rather than host conditioning. The ability to generate decellularized scaffolds populated with recipient-derived endothelium and stromal cells provides a platform for immune self-tolerance by design. In parallel, 3D bioprinting and organ-on-chip technologies are enabling the fabrication of vascularized constructs with controllable cell composition, mechanical properties, and antigenicity [69]. Such constructs could be used not only for reconstructive transplantation but also as preclinical models to study immune tolerance mechanisms in a physiologically relevant environment.
Nanotechnology and biomaterial engineering are also being leveraged to deliver immunomodulatory molecules directly to the graft. Nanoparticle-based systems loaded with rapamycin, IL-10, or TGF-β have been shown to induce local Treg recruitment and suppress effector T-cell infiltration without systemic toxicity [49]. These targeted delivery approaches could synergize with cell-based therapies, such as Tregs or mesenchymal stromal cells (MSCs), enhancing local immune regulation and reducing systemic exposure.

Looking forward, the integration of bioengineered grafts, immune regulatory cell therapies, and molecular monitoring may transform the paradigm of VCA from an immunosuppression-dependent therapy to a precision immunoregulatory reconstruction. The convergence of these disciplines supports a vision of future composite allografts that are immunologically "quiet", biologically integrated, and functionally durable. Achieving this will require close collaboration between transplant immunologists, bioengineers, and reconstructive surgeons, as well as harmonized clinical trials to validate safety, reproducibility, and long-term outcomes.

In summary, the ongoing fusion of decellularization, advanced preservation, and immune engineering represents a decisive step toward sustainable tolerance in VCA. By designing grafts that are intrinsically compatible with the host immune system, the field may ultimately achieve the long-sought goal of functional, rejection-free transplantation without chronic immunosuppression.

CONCLUSIONS

Vascularized composite allotransplantation (VCA) stands at the intersection of reconstructive surgery, transplantation immunology, and regenerative medicine. Over the past two decades, clinical experience has proven that these procedures can restore anatomy, function, and identity after catastrophic tissue loss. Yet, the long-term challenge remains the same: the persistent risk of immune rejection and the burden of lifelong immunosuppression.

Current evidence indicates that acute rejection, predominantly T cell-mediated, remains nearly universal during the first post-transplant year, while chronic rejection, characterized by graft vasculopathy, is a progressive and often irreversible process driven by both cellular and humoral mechanisms. The skin's high immunogenicity, the diversity of tissue components, and frequent pre-existing sensitization in recipients collectively make VCA one of the most complex models of immune recognition in transplantation biology.

Scientific progress, however, is reshaping this landscape. Experimental and early clinical data suggest that immunological tolerance – once viewed as theoretical – can be approached through a combination of mixed hematopoietic chimerism, regulatory T-cell (Treg) therapy, and mesenchymal stromal cell (MSC) modulation. These strategies act at complementary levels: central deletion of alloreactive clones, peripheral suppression of effector responses, and restoration of an anti-inflammatory microenvironment. In parallel, decellularization, recellularization, and machine perfusion technologies offer an engineering solution to the immunologic problem – creating grafts that are structurally viable yet immunologically "quiet".

The convergence of these biologic and bioengineering strategies marks a paradigm shift from pharmacologic immunosuppression toward precision immunoregulation. Future VCA protocols will likely integrate tolerance-inducing cellular therapies, immune monitoring guided by molecular biomarkers, and engineered grafts customized for immunologic compatibility. Such integration may not only prolong graft survival but also allow eventual discontinuation of systemic immunosuppression – a transition from disease management to biological integration.

Ultimately, the success of VCA will depend on multidisciplinary collaboration among surgeons, immunologists, and bioengineers, and on ethically designed clinical trials capable of validating safety, reproducibility, and long-term function. The lessons learned from VCA extend beyond reconstruction: they define the next frontier of transplantation science, where tolerance is engineered, rejection is predictable, and graft survival becomes synonymous with patient recovery.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

BL: A,D,DT
AP: D,W
GDO: S, DT
VC: A, DT

Abbreviations

A: conceived and designed the analysis
D: collected the data
DT: contributed data or analysis tool
S: performed the analysis
W: wrote the paper

Ethical consideration

This study is a literature review and does not involve the collection or use of original data from human or animal subjects. Therefore, ethical committee approval and informed consent were not required. All data were obtained from previously published studies and properly cited.

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