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Review

Sensitization and desensitization of burn patients as potential candidates for vascularized composite allotransplantation

H.J. Klein [a,*], U. Schanz [b], M. Hivelin [c], M. Waldner [a], V. Koljonen [d], M. Guggenheim [a], P. Giovanoli [a], V.S. Gorantla [e], T. Fehr [f,g], J.A. Plock [a,e]

[a] Division of Plastic Surgery and Hand Surgery, Burn Center, University Hospital Zurich, Switzerland
[b] Division of Hematology, University Hospital Zurich, Switzerland
[c] Service de Chirurgie Plastique et Reconstructrice, Hôpital Européen Georges Pompidou – Assistance Publique – Hôpitaux de Paris, Université Paris Descartes, Paris, France
[d] Department of Plastic Surgery, Helsinki University Hospital, Helsinki, Finland
[e] Department of Plastic Surgery and Starzl Transplant Institute, University of Pittsburgh Medical Center, Pittsburgh, USA
[f] Department of Internal Medicine, Cantonal Hospital Graubuenden, Chur, Switzerland
[g] Interdisciplinary HLA Typing Laboratory, University Hospital Zurich, Switzerland

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ABSTRACT

Sensitization describes the acquired ability of the immune system to react to foreign human leukocyte antigens (HLA) by producing antibodies and developing memory cells. In the field of transplantation, recipient preformed HLA antibodies due to previous sensitization have been identified – beneath ABO incompatibility – as a major factor for acute graft rejection. Several reasons for sensitization have largely been studied, such as previous blood transfusions, pregnancies or former transplants. Recent studies indicate that the use of assist devices (e.g. ECMO) or cadaveric skin allotransplantation providing temporary coverage in burn patients may lead to additional sensitization. As vascularized composite allotransplantation (VCA) has become a rapidly advancing therapeutic option for reconstruction of complex tissue defects in burns, it seems even more important to become familiar with immunological principles and to be cautiously aware of both sources of sensitization and therapeutic concepts in burns avoiding sensitization. This may also include emergency VCAs in burn patients as potential strategy for early definitive reconstruction avoiding procedures triggering HLA antibody formation.

We hereby provide an overview on current evidence in the field of pre- and peritransplant sensitization, followed by posttransplant strategies of desensitization and their potential impact on future treatments of burn patients.

* *Corresponding author at*: University Hospital Zurich, Division of Plastic Surgery and Hand Surgery, Raemistrasse 100, 8091 Zurich, Switzerland. Tel.: +41 044 255 111; fax: +41 044 255 8977.
E-mail address: holger.klein@usz.ch (H.J. Klein).
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Contents

1. Introduction

Vascularized composite allotransplantation (VCA) is a rapidly advancing therapeutic option for reconstruction of complex tissue defects [1–4]. Major trauma to the face and extremities frequently leaves massive soft and bony tissue defects that are not amenable to conventional reconstruction. Functional or esthetic outcomes may be suboptimal and may be associated with substantial morbidity. VCA facilitates the ideal goals of reconstructive surgery – ''to replace like with like''. However, advancement of VCA as a routine reconstruction option is hampered by the burden of immunosuppression for long term graft acceptance [5].

Since the inception of clinical VCA over a decade ago, burn victims have been identified as immunologically complex patients for these procedures [6,7]. This population may be prone to sensitization for various reasons, which has been an exclusion criterion for many VCA programs around the world. Different concepts of both desensitization as well as induction and maintenance immunosuppression have been investigated and implemented in solid organ transplants [8–13], while similar protocols or experiences in VCA are limited [13]. The principles of sensitization and desensitization in burns and VCA appear largely uncharted [14,15].

Sensitization describes the acquired ability of the immune system to react to foreign human leukocyte antigens (HLA) by producing anti-HLA antibodies and developing memory cells. In the field of transplantation, donor-specific, preformed recipient HLA antibodies (DSA) have been identified – beneath ABO incompatibility – as a major risk factor for hyperacute and acute allograft rejection [14,16–20]. Several reasons for sensitization have been identified, such as previous blood transfusions, pregnancies or former transplants. Recent studies indicate also that the use of cardiac assist devices (e.g. extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD)) or even cadaveric skin allotransplantation providing temporary coverage in burn patients may lead to a primary or additional sensitization [15,21,22].

About 35% of all patients on a renal transplant waiting list in the US are HLA-sensitized due to previous transplantation, blood transfusions or pregnancies [23]. Historically this led to the introduction of anti-HLA antibody screening and pre-transplant complement-dependent cytotoxcitiy (CDC) crossmatch testing to avoid antibody-mediated rejection [24,25]. Successful solid organ transplantation across HLA and/or ABO barriers – emerging in the 1980s – using now refined desensitization protocols aiming at reduction of pre-existing antibodies to a level that qualifies for successful engraftment, have stimulated the interest in grafts from HLA-incompatible or immunologically less favorable donors [26,27]. Different strategies to remove pre-existing antibodies have been tested by using techniques like plasmapheresis and immunoabsorption, while other protocols using splenectomy or the application of antibodies (e.g. rituximab) or intravenous immunoglobulins (IVIG) target anti-HLA antibodies indirectly [20]. The trend of immunologically incompatible organ replacement with good short-term results is meanwhile widespread for kidney transplantations based on a broad understanding of the principles of sensitization and desensitization [28–32].

In the history of VCA, transplantations have been performed with HLA mismatch between donor and recipient, whereas negative CDC crossmatch and ABO compatibility remain a prerequisite [33]. The prevalence of sensitization in patients awaiting VCA is thought to be essentially lower than in patients being scheduled for solid organ transplantation for various reasons. Devastating trauma to the hand or face qualifying for VCA mostly happen to previously healthy, young, often male patients with a low risk of previous sensitization. According to the literature, 80% of the patients who have received reconstructive VCAs are male with an average age of 34 years for face transplantation and 84% of the patients with hand transplantation are male with a median age of 32 years [34]. The average age for renal transplantation