Transplant International

INVITED COMMENTARY

Immunosuppression in vascularized composite allotransplant: the search for an effective and safe treatment continues

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Transplant International 2020; 33: 1291–1293

Received: 24 April 2020; Accepted: 24 April 2020

Vascularized composite allotransplants (VCA) including hand, face, and most recently transplants of reproductive organs represent unique, life-changing procedures that have been established in centers around the world, albeit in small numbers [1].

One of the major impediments in moving VCA transplants forward has been the necessity of immunosuppression for a procedure that is life-enhancing rather than lifesaving. Indeed, side effects of immunosuppression have been broad in VCA, just like in solid organ transplant recipients. Of additional relevance, unwanted effects of immunosuppressants may also reach a different level of concern for a lifelong immunosuppression in face and hand transplantation compared to short-term treatments in temporary grafts such as uterine transplants.

Acute rejections have been frequent in VCA, potentially linked to the augmented immunogenicity of skin components [2]. Moreover, chronic graft failure and antibody-mediated rejections, that had not been reported during the initial experiences with VCA, have become a clinical reality with increasing VCA volumes and prolonged observation times. Notably, mechanisms that contribute to long-term graft failure and late antibody-mediated rejections in VCA remain unclear with potential contributions of noncompliance or insufficient immunosuppression [3].

Exploring novel and calcineurin inhibitor (CNI)-free immunosuppression that may specifically target immune cells involved in skin pathologies while preventing antibody-mediated responses provides therefore an interesting and novel rationale.

Belatacept is a soluble fusion protein composed of a modified version of the extracellular domain of cytotoxic T lymphocyte antigen 4 linked to the Fc domain of a human IgG1 antibody. The co-stimulatory blockade agent belatacept selectively inhibits T-cell activation with lower de novo and overall frequencies for DSAs [4]. Dr. Cendales' group had previously reported on a conversion from a CNIs-based immunosuppressive regimen to belatacept in clinical VCA, improving renal function [5].

doi:10.1111/tri.13629

The same group has also applied belatacept as a *de novo* treatment without CNIs in clinical VCA [6].

Data from solid organ transplantation have shown increased numbers of acute rejections when using belatacept, potentially related to an insufficient blockade of alloreactive memory T cells [7].

In the current issue of "Transplant International," Atia *et al.* [8] report on a novel immunosuppressive approach utilizing belatacept in addition to either ustekinumab or secukinumab, two agents inhibiting Th17 cells and their signature cytokine IL-17. Their approach included a steroid taper, however no additional T-cell targeting therapy. This immunosuppressive regimen was tested in a sensate osteomyocutaneous radial forearm flap in non-human primates (NHP, three animals/group). Outcomes were compared to a historic group of NHP that received a standard immunosuppression with tacrolimus, MMF, and methylprednisolone.

Ustekinumab has been shown to inhibit cutaneous Th17 cell proliferation and maturation; secukinumab, a human monoclonal antibody, targets IL17A. With Th17 playing a central role in dermatological immunity and skin being a critical component of the augmented immunogenicity in face and hand transplantation, this immunosuppressive approach appears of interest. Moreover, blocking IL-17 deficiency has previously shown to prolong renal allograft survival in a fully mismatched kidney transplant model [9].

Interestingly, co-stimulatory blockade combined with an approach targeting Th17/IL-17A provided "negative" results with grafts in all groups rejected by 10–11 days, significantly earlier compared to the survival in historic controls (mean 31 days). Notably, graft survival was significantly lower, even so numbers of IL-17a+ cells and the intensity of IL-17a expression had been significantly reduced in both dermis and hypodermis in NHP that had been treated with Th-17/IL-17-targeting agents.

Clearly, negative results are less "sexy," nevertheless as important more glamorous "positive" data. The involvement of Th17 in organ rejection is indeed complex and not entirely understood. Th17 cells have not only been linked to early alloimmune responses but also to innate immunity and chronic graft failure. Both, Th1 and Th17 cells express CD28; however, Th17 cells express significantly higher levels of coinhibitory CTLA-4 [10], thus potentially augmenting Th17 proliferative responses. Moreover, Th17 cells rely heavily on non-CD28 co-signaling pathways for optimal function [11].

Thus, while Th17 responses may be of relevance in VCA and skin rejection, an initial and more potent immunosuppression preventing Th1 and memory T-cell responses may be necessary to support the efficacy of Th17/IL-17 inhibition. Does that mean that we need to go back to the drawing board? We certainly need more information on the biology of VCA-specific alloimmune responses. Until then, we remain to be stuck in VCA with applying the standard immunosuppression that we have for solid organ transplantation. Previously successful attempts achieving tolerance in preclinical VCA models [1] or ways to reduce/minimize immunosuppression in clinical VCA [12] may provide some glimmer of hope. Of interest may also be future approaches that will include combinatorial treatments targeting donors, the graft itself during preservation/perfusion, and VCA recipients. As timing of TH17/IL-17-targeted therapy appears critical, treatments already starting in the donor and the graft combined with a potent inhibition of alloreactive T cells in recipients may get Th17/IL-17 inhibition back in the race on an optimized immunosuppression in VCA.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

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