

Meeting Report of the 13th Congress of the International Society of Vascularised Composite Allotransplantation

Annemarie Weissenbacher^{1,2} MD, Linda Cendales³ Prof, Emmanuel Morelon⁴ Prof, Palmina Petruzzo^{5,6} Prof, Gerald Brandacher⁷ Prof, Peter J. Friend¹ Prof, Vijay Gorantla⁸ Prof, Christina Kaufman⁹ Prof, Johanna Krapf¹⁰ MD, Lawrence Scott Levin¹¹ Prof, Georgios Vrakas¹ MD, PhD, Stefan Schneeberger² Prof

¹ Oxford Transplant Centre, Nuffield Department of Surgical Sciences, Oxford University Hospitals, Oxford, UK

² Department of Visceral, Transplant and Thoracic Surgery, Innsbruck Medical University, Innsbruck, Austria

³ Department of Surgery, Duke University, Durham, NC, USA

⁴ Department of Transplantation, Nephrology and Clinical Immunology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

⁵ Department of Surgery, University of Cagliari, Cagliari, Italy

⁶ Department of Transplantation, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

⁷ Department of Plastic and Reconstructive Surgery, Johns Hopkins School of Medicine, Baltimore, MD, USA

⁸ Departments of Surgery, Ophthalmology and Bioengineering, Wake Forest School of Medicine, Wake Forest Institute of Regenerative Medicine, Winston Salem, NC, USA

⁹ Christine M. Kleinert Institute, Louisville, KY, USA

¹⁰ Department of Plastic and Reconstructive Surgery, Innsbruck Medical University, Innsbruck, Austria

¹¹ Department of Surgery and Orthopaedic Surgery, Division of Plastic and Reconstructive Surgery, Children's Hospital of Philadelphia, Perelman, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence

Annemarie Weissenbacher, MD

Oxford Transplant Centre, Nuffield Department of Surgical Sciences

University of Oxford

Old Road, Oxford, OX3 7LE, United Kingdom

Tel.: +447481147692

E-mail: annemarie.weissenbacher@nds.ox.ac.uk

Abstract

The International Society of Vascularised Composite Allotransplantation (ISVCA) held its 13th congress “Defining Success” in October 2017 in Salzburg, Austria. A total of 122 delegates from 22 countries representing five continents attended the conference. The theme strived to provide pathways to accomplish best possible outcomes in this unique and multifaceted field of transplantation. ‘Ignite talks’, a new feature introduced for the first time at the Salzburg meeting served as key elements for productive discussions on both congress days. The “ignitors” had been selected as experts from Europe, the Americas and Asia in VCA and neighbouring disciplines and provided a global perspective of their topic. Post-transplant treatment regimens, including the most burdensome side effects of immunosuppressants in addition to novel and future therapeutic options were discussed in depth. An additional ethics symposium summarized and advanced topics that had been discussed during the first

international workshop on bioethical challenges in reconstructive transplantation held earlier in 2017.

Introduction

122 delegates including surgeons, transplant physicians, pathologists, immunologists, paediatricians, gynaecologists, urologists, specialists in physical medicine and rehabilitation and ethicists from 22 countries and five continents attended the conference. The Salzburg 2017 congress summarized the current state of the art and aimed to develop a unified strategy to advance VCA. It was felt as critically important in this still relatively new field to define clear endpoints and to discuss modalities paving the way for best possible outcomes. Representatives of ISVCA, The Transplantation Society (TTS), the American Society for Reconstructive Transplantation (ASRT) and the VCA committee of the European Society for Organ Transplantation (ESOT) actively participated in the conference. The ethics symposium mainly addressed the question how VCA centres can best fulfil the ethical obligation to identify, select and support candidates in VCA and achieve best outcomes.

‘Igniting’ progress and discussion:

Clinical progress of new areas in VCA, refined indications and selection criteria, immunomodulatory protocols, UNOS/OPTN oversight, in addition to scientific progress related to immune tolerance, immune monitoring, improved preservation techniques, localized drug delivery, and novel aspects of neuroregeneration were presented. An update was provided on the progress of VCA in children, one of the most recent achievements. The world’s first bilateral paediatric hand transplant had been performed at Children’s Hospital of Philadelphia with support by a surgical team from UPenn in 2015 (1). The 8-year-old recipient had previously received a living donor kidney transplantation in 2011 following sepsis induced renal failure. His progress after the bilateral hand transplantation has been promising resulting in an overall very active, now 10-year old boy. He has had six acute rejection episodes in the absence of de novo donor specific antibodies (dnDSA) so far and a stable kidney function.

Talks on “America, Europe, Asia and beyond – a global approach for VCA” addressed, i), quality criteria and standards for VCA; ii), feasibility of donation and VCA allocation in Asia; iii), waiting lists management in addition to donation and allocation of VCA nationally and internationally within Europe. A well-structured and informative bio- and databank will be critical in moving the field forward. The Oxford program has spearheaded this endeavour and shared their experience in building a national/international biobank for quality in organ donation (QUOD) in solid organ transplantation (SOT). This initiative combines the collection of human samples matched with a clinical data base in organ donation and transplantation (2). Critical for the success of a biobank program in the field of VCA are, i), an international consortium and scientific platform, ii), a robust infrastructure, iii), supporting basic

research in donation and transplantation including the identification of injury and repair pathways, and v), validation of predictive outcome markers.

Immunosuppression obviously represents one of the most pressing issues in VCA and pros and cons of minimization protocols have been discussed at length. Improved outcomes in VCA could possibly be achieved with better HLA and CMV matching, an improved understanding of unspecific injuries before or after transplantation augmenting innate and adaptive immunity in addition to novel approaches in graft perfusion/preservation and eventually graft pre-treatment immunomodulation. Strategies for monitoring may be improved by sentinel flaps, ultrasound, biomicroscopy and detection of meaningful biomarkers. With respect to immunosuppressive drug therapy, reduction of immunosuppression with or without cell based therapy were addressed. Both mixed chimerism and transient chimerism with reduced IS treatment were discussed. Overall, caution was recommended with overly aggressive minimization protocols potentially linked to a higher incidence of acute rejection episodes, an increased risk of chronic rejection and the development of dnDSA.

Graft losses have been reported due to chronic vasculopathy in both hand and face transplantation.

Sensory recovery after hand transplantation remains an important topic since lack of sensibility is the dominant limitation of prosthetic devices. It was clearly stressed that the success of VCA transplants depends on both motor and sensory restoration and the urgent need to establish standard methods for clinical assessment of sensory restoration in VCA.

Defining success for non-life saving procedure represents an important aspect in VCA and was discussed in presentations on hand, face, abdominal wall transplants, uterus and penis transplantation. Implementing DALY (disability adjusted life years, a modification of QUALY/quality adjusted life years) in the assessment and decision making was considered useful for face transplantation. The Oxford experience for abdominal wall transplantation did not only demonstrate surgical success but also the utility of sentinel skin flaps as a surrogate marker of infection and rejection. Other highlights from this interactive session were the presentations from the Gothenburg group on uterus transplantation (UTx) and the group from Cape Town on penile transplantation.

The Gothenburg group presented eight healthy babies with additional pregnancies at several stages. In addition to their unique clinical success, the group also presented their broad experimental work in uterus transplantation (3).

Worldwide, three penis transplants have been performed, all with surgical and functional success. Penis transplantation, based on the first successful case in Cape town, South Africa has been shown to be ethical and feasible (4).

Defining graft survival in VCA remains a challenge with graft survival and function being multifaceted. Functional assessment depends on the type of VCA: integrity for abdominal wall, dexterity in addition to sensation and motoric recovery for limb transplants (5), aesthetic and functional recovery, including aesthetic results for face transplants, the delivery of a healthy baby in UTx and sexual function after penile transplantation. Although most of the outcome criteria can be validated objectively, subjective criteria of graft outcome (e.g. appearance) influencing the patients' satisfaction and their quality of life remain.

The definition of failure and success is expected to change over time as the field progresses. While a healthy baby seems to be a clear endpoint in UTx, functional success is more difficult to define in other areas of VCA.

Chronic rejection is gaining relevance with more VCA transplants achieving long-term graft outcomes. The definition of chronic rejection in VCA may need to be better classified/defined by the type of VCA and/or location and this discussion will help to update the current Banff classification (6) that is on the way.

Participants also felt that, similar to other organs, preventing imbalances of immunosuppression and avoidance of dnDSA may help to ameliorate chronic alloimmune responses.

Summary

VCA remains a unique, very diverse and young field in transplantation. The recent ISVCA "Defining Success" congress attempted to define best possible outcomes and the most promising results.

There were two main messages arising from the presentations and discussions during the congress.

First, VCA is a field that continues to grow with more centres starting VCA programmes and with additional novel procedures taking place (paediatric, uterine and penile transplantation).

Second, indications and immunosuppressive treatment should be considered carefully and in the view of chronic allograft changes, which are often the leading cause of late graft losses.

Overall, the field is expected to move forward in delineating objective outcome parameters in an organ-specific fashion.

References

- 1) Gaetz W, Kessler SK, Roberts TPL, et al. Massive cortical reorganization is reversible following bilateral transplants of the hands: evidence from the first successful bilateral pediatric hand transplant patient. *Ann Clin Transl Neurol* 2017; doi: 10.1002/acn3.501
- 2) <https://www.nds.ox.ac.uk/research/quod>

- 3) Livebirth after uterus transplantation. Brännström M, Johannesson L, Bokström H, et al. Lancet 2015; 385: 607-616.
- 4) Penile Allotransplantation for penis amputation following ritual circumcision: a case report with 24 months of follow-up. Van der Merwe A, Graewe F, Zühlke A, et al. Lancet 2017; 390: 1038-1047.
- 5) <https://www.handregistry.com>
- 6) Cendales LC, Kanitakis J, Schneeberger S, et al. The Banff 2007 working classification of skin-containing composite tissue allograft pathology. Am J Transplant 2008; 8: 1396-1400.