



## The Innsbruck Hand Transplant Program: Update at 8 Years After the First Transplant

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### ABSTRACT

We herein provide an update on two bilateral hand and one bilateral forearm transplants with emphasis on immunosuppression (IS), function, morphology, and graft vascular changes at 8 years and 2 years after bilateral hand and 5 years after bilateral forearm transplantation. Between March 2000 and May 2006, three patients underwent bilateral hand or forearm transplantation at our institution. Following induction therapy with antithymocyte globulin (ATG) ( $n = 2$ ) or alemtuzumab ( $n = 1$ ), tacrolimus, prednisolone  $\pm$  mycophenolate mofetil (MMF) were given for maintenance IS. Later, tacrolimus ( $n = 1$ ) or MMF ( $n = 1$ ) was replaced by sirolimus/everolimus for long-term IS. Clinical follow-ups with evaluation of hand function, skin biopsies, X-ray, ultrasound, angiography, computed tomography angiography, electrophysiological studies, and somatosensory evoked potentials were performed at regular intervals. Three, six, and three rejection episodes were successfully treated with bolused steroids, anti-CD25 or anti-CD52 antibodies. Subsequently, skin histology remained normal without any evidence of chronic rejection. Hand function continuously improved during the first 3 years and since then remained stable with minor improvements. Investigation of hand arteries revealed no signs of occlusion or stenosis. Motor and intrinsic hand muscle function continues to improve in all patients. Protective sensation was observed in all patients; however, discriminative sensation was only accomplished after hand but not forearm transplantation. No life-threatening adverse events occurred. Despite immunologic challenging postoperative courses, patients are now free of rejection with moderate levels of IS and good functional results. No signs indicating chronic rejection have been encountered.

**R**ECONSTRUCTIVE TRANSPLANTATION represents a valid therapeutic option after the loss of a hand, forearm, or digits and holds potential to become a novel therapeutic entity in reconstructive surgery and transplantation

medicine. Early results in reconstructive transplantation are promising.<sup>1</sup> Nevertheless, the risks associated with currently used long-term immunosuppression (IS) need to be weighed against the expected benefits for each individual patient.

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Recent reports provide evidence that the principle goals of hand transplantation, namely, to achieve good motor function together with discriminative sensation, can be achieved and result in patient satisfaction far superior to myoelectrical prostheses.<sup>2-6</sup> Beyond conventional outcome measures, hand or face transplantation is the only therapeutic option to achieve full body integrity after devastating injuries, a gratification which, in our experience, significantly contributes to patient contentment.

We have previously reported the 5-year outcome after the first bilateral hand transplantation performed in Austria and the 3-year outcome after the first bilateral forearm transplantation.<sup>7,8</sup> Here we have provided an update on the clinical courses and functional outcomes of all three patients transplanted in Innsbruck, Austria, with emphasis on IS, function, morphology, and graft vascular changes at 8 years and 2 years after bilateral hand and 5 years after bilateral forearm transplantation.

## PATIENTS AND METHODS

Detailed descriptions of patient and donor selection, surgical procedures, and clinical courses of the first hand and the forearm transplantation performed in Innsbruck were published earlier.<sup>7,8</sup> In brief, the first patient was a 47-year-old policeman who lost his hands when he attempted to deactivate a bomb as part of his job in 1994. The forearm transplant recipient was a 41-year-old electrical engineer who lost his hands and two-thirds of his forearms in an electrical current accident, again when performing his duty as an engineer for the Austrian railway company. The third most recent patient was a 23-year-old student from the Ukraine who also lost his both hands in a bomb blast in the year 2000. The first two patients were equipped with myoelectrical prosthesis prior to transplantation while the third patient did not consider myoelectrical prosthesis as a suitable replacement for the missing hands.

### Immunologic Risk Profile

Preformed panel-reactive HLA antibodies were only present in patient 1 (5%). Donor/recipient HLA match was 0/6, 2/6, and 3/6 in patients 1, 2 and 3, respectively. The pretransplant lymphocytotoxic crossmatch was negative in all three patients. Cold ischemia upon transplantation was  $162 \pm 22$  minutes (mean  $\pm$  standard deviation).

### Surgery

Transplantations were performed by teams of the Department of Plastic and Reconstructive Surgery and Traumatology in March 2000, February 2003, and May 2006.<sup>2,7-9</sup> In the first case, a skin autograft was placed to the left forearm shortly after the transplant and multiple arteriovenous fistulas were occluded at 6 months. The second patient received a full forearm allograft including forearm muscles. A small split-thickness skin graft was used to cover a small defect at the wound on day 3. Cosmetic surgery for scars was performed in August 2005. The third hand transplantation was performed at the level of the mid forearm, and again small autografts were used to cover small defect at both forearms. Decompression for a hematoma and tissue swelling had to be performed 1 week after transplantation.

### Immunosuppression

IS in the first two patients included induction therapy with antithymocyte globulin (ATG) and alemtuzumab (Campath-1H) in the third patient. For maintenance IS, patients received tacrolimus and prednisone in all cases and mycophenolate mofetil (MMF) in the first two cases. Reduction of the overall amount of IS including steroid withdrawal was cautiously aimed for in all patients. Conversion from tacrolimus to sirolimus or everolimus is part of the long-term treatment plan.

### Rehabilitation Program

A detailed description of the specific rehabilitation program and assessment measures of hand function as well as electrophysiological studies were previously published.<sup>7</sup>

### Imaging Modalities

Imaging modalities for graft vessels, nerves, muscles, and tendons included ultrasonography, angiography and computed tomography angiography with three-dimensional reconstruction of graft vessels.<sup>7</sup>

### Functional Magnetic Resonance Imaging

Using a 1.5-Tesla magnetic resonance (MR) scanner (Magnetom Avanto, Siemens Erlangen, Germany) and a head coil with eight arrays, functional MR images were collected with the help of a single-shot echoplanar imaging sequence. Anatomic images were acquired as a set of 160 contiguous sagittal slices by using T1-weighted 3D-magnetization prepared rapid acquisition gradient echo sequences. Patients underwent four consecutive functional MR imaging measurements with rest and motion paradigms including finger typing and softball compression of both hands.

## RESULTS

### Immunologic Complications

Three, six, and three rejection episodes were observed during the 8-, 5- and 2-year follow-ups. Time of first rejection was days 55, 9, and 51 in patients 1, 2 and 3, respectively. In patient 1, all acute rejections were histologically mild (grade I-II), responding promptly to steroid treatment. IS was gradually reduced to low-dose sirolimus monotherapy (trough level 6-7 ng/mL). Currently, the patient is slowly and cautiously being weaned from the remaining immunosuppression.

Rejections in the forearm transplant recipient were more severe and resistant to steroid and ATG treatment in one case.<sup>10</sup> A total of six rejections were treated with topical and systemic steroids, basiliximab, alemtuzumab (twice), and transient increases in tacrolimus dose. The patient has now been free of any signs of rejection for over 2 years.

In the third patient, two early rejections were observed on days 51 and 60. While the first rejection was treated successfully with intravenous steroids, the second was atypical with regard to its appearance and manifestation at the palm of the hand. This type of rejection has also been observed in three other hand transplant recipients; a comprehensive report describing this phenomenon was published recently.<sup>9</sup> Treatment with alemtuzumab was effec-

tive; the lesions disappeared. However, a third rejection episode occurred on day 601 and was resistant to steroid treatment, requiring alemtuzumab. Since then, no further immunologic complications have been encountered in any patient. The histology of all recent protocol biopsies was normal without any histopathologic evidence of lymphocytic infiltration with no additional alterations in skin morphology. Neither systemic nor intragraft chimerism were observed in any patient.

#### Functional Outcome

In our first patient, hand function and sensitivity continuously improved during the first 5 years and remained stable with minor improvement thereafter.<sup>7</sup> Eight years after transplantation, hand function in this patient is outstanding. He is able to use his hands symmetrically, performing all activities of daily life. Furthermore, advanced fine motor skills allow him to perform manually difficult tasks such as repair jobs on his motorbike. The strength of the intrinsic muscles measures between M3 and M5 according to British Medical Council Scale, respectively. Total active range of motion (TAROM) of the right thumb shows 81° and 182° for the left index finger, which illustrates a slight decrease compared to measurements at 7 years after transplantation. Results of the 2-point discrimination test further support this observation. The current DASH (disabilities of the arm, shoulder and hand) score is 34.

Motor function continuously improved in the forearm transplant patient during the first 3 years, resulting in satisfactory hand function. According to the patient's subjective perception, hand function is superior to that achieved with myoelectrical prostheses. He emphasized the benefit of sensibility. Intrinsic hand muscle function, first observed at 16 months, continues to improve. Despite the recovery of hot and cold discrimination first detected at 6 months after transplantation, overall sensitivity remains poor with no detectable 2-point discrimination.<sup>8</sup> Sensory responses from the median nerve were first recorded at 4 years after transplantation. At 5-year follow-up, the outcome of the Kapandji opposition test showed 4 points on the right side and 2 points on the left side. Grip strength measured 6.8 kg in position 2 on the right side and 5.5 kg on the left side. However compared with results after hand transplantation, fine motor skills are slightly inferior in our forearm transplant patient.

Two years after hand transplantation, our third patient is still undergoing intensive rehabilitation on an outpatient program, 3 times a week for 5 hours. When reading the functional outcome, rehabilitation was complicated by blindness and therefore the lack of visual feedback. Despite this challenge, the patient showed clinical and electromyographical signs of intrinsic muscle recovery. The Action Research Arm Test score was 35 on the right side and 23 on the left side. Actual TAROM of the index finger on the right side was 124° and 89° of the left thumb.

Nerve conduction studies demonstrated a progressive increase in compound motor and sensory evoked poten-

tials starting at 6 months after transplantation in all three patients. Reinnervation steadily progressed, and long-duration polyphasic potentials were recorded after 3 years. Motor as well as sensory action potentials further increased at 4 and 5 years after transplantation, which refutes earlier expectations that nerve regeneration would occur only during the first postoperative year.

Cortical motor activation patterns following hand transplantation have been previously described in detail.<sup>11</sup> However, reorganization of the motor and somatosensory cortex as assessed by functional MR imaging at 5 years after transplantation showed typical activation in the motor and primary as well as secondary (lobulus parietalis inferior) somatosensory cortex after bilateral forearm transplantation.

#### Chronic Vascular Changes

No radiomorphological changes in the graft vessels were observed during the observation period in all three patients. Specifically, no luminal narrowing, as an indirect sign for myointimal proliferation, was observed as reflected by stable proportions and consistent perfusion of all tissue components up to 8 years after transplantation.

#### Infectious Complications

Cytomegalovirus (CMV) infection was observed in all three patients. In the first two cases, CMV disease resistant to valgancyclovir was treated with cidofovir. Hyperlipidemia and noninsulin-dependent diabetes mellitus were observed in the first patient. In the forearm transplant recipient, a tissue-invasive fungal infection with *Alternaria* was treated by local excision, a short course of amphotericin, and itraconazole.<sup>12</sup> Hypertension resulting in a severe headache was treated with rilmenidin, losartan, losartan-hydrochlorothiazide, doxazosin, and urapidil. Papilloma virus-associated warts were treated with topical cidofovir ointment in this patient.

#### Current Immunosuppression

The current immunosuppressive regimen in our patients consists of sirolimus with targeted trough levels of 6 to 8 ng/mL in combination with MMF 2 g/d in the first patient FK506 (trough levels 6–8 ng/mL) in combination with everolimus (trough levels 4–6) in the second forearm transplant patient, and FK506 (trough levels 10–12 ng/mL), MMF (1 g/d), and prednisone (10 mg/d) in the third hand transplant recipient. Overall, IS was gradually tapered to acceptable levels in all three patients to levels comparable to or even less than those in kidney transplantation patients at similar times after transplantation.

#### DISCUSSION

Despite immunologically challenging postoperative courses, all three patients after hand or forearm transplantation are now free of rejection with moderate levels of IS and good functional results. No signs of chronic rejection have been

encountered at up to 8 years after transplantation. Bilateral hand as well as forearm transplantation therefore can be considered a valid therapeutic option for a selected group of patients at this point.

Currently, all patients receive IS similar to that used for solid organ transplantation. This treatment seems to be sufficient to achieve long-term allograft survival in hand transplantation. Mammalian target of rapamycin inhibitors seem to be suitable for long-term IS due to their potential to prevent or slow down the progression of chronic rejection and their toxicity profile.<sup>13,14</sup>

However, CMV infections in particular remain a challenging problem in composite tissue allotransplantation (CTA): high levels of IS are known to be the most important risk factor.<sup>15</sup> All patients experienced CMV infections during the early postoperative periods. A close correlation was observed between virus replication and rejection in some cases.<sup>15</sup> Therefore, whenever possible, CMV donor-recipient mismatch should be avoided in hand transplantation; prophylaxis with valgancyclovir and anti-CMV hyperimmunoglobulin are considered mandatory.<sup>15</sup> Of note, at later phases paralleled by a significant reductions in maintenance IS, we did not encounter any CMV replication or CMV disease.

In all patients, hand function and sensitivity continuously improved during the first 3 years, remaining stable with minor improvements thereafter. Most strikingly, both motor as well as sensory action potentials still increased at more than 5 years after transplantation, suggesting that nerve regeneration also occurs late after CTA, and not, as previously supposed, only during the first postoperative year. However, it still remains unknown whether long-term function and survival are limited by chronic rejection as occurs in solid organ transplantation.<sup>16</sup> Radiomorphological studies as well as histological examination of samples from compartments other than the skin retrieved upon the surgical intervention for scars were normal with only a mild perivascular lymphocytic infiltrate, allowing for cautious optimism since over the years no luminal narrowing as an indirect sign of myointimal proliferation was observed as reflected by stable proportions and consistent perfusion of all tissue components.

In conclusion, all of our patients are currently pleased with the sensomotoric and cosmetic outcomes. They consider their daily lives "as almost completely normal." They consider hand and forearm transplantation as a means to significantly improve their quality of life. Although conclusive statements cannot be made at this point, the series of three patients presented herein provide evidence that long-

term graft survival with excellent function seems realistic in composite tissue allografts

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#### REFERENCES

1. Lanzetta M, Petruzzo P, Dubernard JM, et al: Second report (1998–2006) of the International Registry of Hand and Composite Tissue Transplantation. *Transpl Immunol* 18:1, 2007
2. Margreiter R, Brandacher G, Ninkovic M, et al: A double-hand transplant can be worth the effort. *Transplantation* 74:85, 2002
3. Jones JW, Gruber SA, Barker JH, et al: Successful hand transplantation. One-year follow-up. Louisville Hand Transplant Team. *N Engl J Med* 343:468, 2000
4. Dubernard JM, Petruzzo P, Lanzetta M, et al: Functional results of the first human double-hand transplantation. *Ann Surg* 238:128, 2003
5. Piza-Katzer H, Ninkovic M, Pechlaner S, et al: Double hand transplantation: functional outcome after 18 months. *J Hand Surg [Br]* 27:385, 2002
6. Piza-Katzer H, Ninkovic M, Pechlaner S, et al: Double hand transplantation: functional outcome after four years Renner A, ed. *Bologna: Medimond; 2004*, p 113
7. Schneeberger S, Ninkovic M, Piza-Katzer H, et al: Status 5 years after bilateral hand transplantation. *Am J Transplant* 6:834, 2006
8. Schneeberger S, Ninkovic M, Gabl M, et al: First forearm transplantation: outcome at 3 years. *Am J Transplant* 7:1753, 2007
9. Schneeberger S, Gorantla VS, van Riet RP, et al: Atypical acute rejection after hand transplantation. *Am J Transplant* 8:688, 2008
10. Schneeberger S, Kreczy A, Brandacher G, et al: Steroid- and ATG-resistant rejection after double forearm transplantation responds to Campath-1H. *Am J Transplant* 4:1372, 2004
11. Brenneis C, Löscher WN, Egger KE, et al: Cortical motor activation patterns following hand transplantation and replantation. *J Hand Surg [Br]* 30:530, 2005
12. Bonatti H, Lass-Flörl C, Zelger B, et al: *Alternaria alternata* soft tissue infection in a forearm transplant recipient. *Surg Infect (Larchmt)* 8:539, 2007
13. Eisen HJ, Tuzcu EM, Dorent R, et al: Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 349:847, 2003
14. Augustine JJ, Bodziak KA, Hricik DE: Use of sirolimus in solid organ transplantation. *Drugs* 67:369, 2007
15. Schneeberger S, Lucchina S, Lanzetta M, et al: Cytomegalovirus-related complications in human hand transplantation. *Transplantation* 80:441, 2005
16. Nankivell BJ, Chapman JR: Chronic allograft nephropathy: current concepts and future directions. *Transplantation* 81:643, 2006