Published online: 2019-07-09

Original Article

First two bilateral hand transplantations in India (Part 4): Immediate post-operative care, immunosuppression protocol and monitoring

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ABSTRACT

Introduction: Being able to counter immune-mediated rejection has for decades been the single largest obstacle for the progress of vascular composite allotransplantation (VCA). The human immune system performs the key role of differentiating the 'self ' from the 'non-self '. This, although is quintessential to eliminate or resist infections, also resists the acceptance of an allograft which it promptly recognises as 'non-self'. **Materials and Methods:** Pre-operative evaluation of the recipient evaluation included immunological assessment in the form of panel reactive antibodies (PRA), human leucocyte antigen (HLA) typing, donor-specific antibody detection assays (DSA) and complement-dependent cytotoxicity assays (CDC). Induction immunosuppression was by thymoglobulin and the maintenance by the standard triple-drug therapy. **Results:** Both the recipients were managed by the standard triple drug therapy and have had only minor episodes of rejections thus far which have been managed appropriately. **Discussion:** Induction immunosuppression was by thymoglobulin and the maintenance by the standard triple-drug therapy. Various groups have tried various other formulations and regimes as well. **Conclusion:** A comprehensive plan has to be drawn up for immunological screening, selection and the post-operative immunosuppressant usage. The ultimate goal of these immunosuppression modalities is to achieve a state of donor-specific tolerance.

KEY WORDS

Composite tissue allotransplantation; hand transplantation; immunosuppression; vascular composite allotransplantation

Access this article online	
Quick Response Code:	Website: www.ijps.org
	DOI: 10.4103/ijps.IJPS_96_17

How to cite this article: Iyer S, Sharma M, Kishore P, Mathew J, Janarthanan R, Reddy R, *et al*. First two bilateral hand transplantations in India (Part 4): Immediate post-operative care, immunosuppression protocol and monitoring. Indian J Plast Surg 2017;50:168-72.

INTRODUCTION

Being able to counter immune-mediated rejection has for decades been the single largest obstacle for the progress of vascular composite allotransplantation (VCA). The human immune system performs the key role of differentiating the 'self' from the 'non-self'. This, although is quintessential to eliminate or resist infections, also resists the acceptance of an allograft which it promptly recognises as 'non-self'. To counter this, various immunosuppressive agents are used. Unfortunately, these are associated with their own share of side effects on account of a curbing of the immune system rendering the body highly susceptible to infection, various systemic toxicities and at times even malignancy.

Traditional immunosuppression regimes include the 'triple drug therapy' with tacrolimus, mycophenolate mofetil and steroids. Recently, immunosuppression induction using lymphodepleting agents such as thymoglobulin and alemtuzumab have led to a significant reduction in the requirement of maintenance steroid dose and in some cases even permitting monotherapy maintenance. This article reports the regime that was used in the first two double hand transplants in India. The monitoring of the patients and the management of rejection episodes are described. Furthermore, the medical issues during the immediate post-operative period are also discussed.

MATERIALS AND METHODS

Preoperative evaluation

Preoperative evaluation of the recipient evaluation included immunological assessment in the form of panel reactive antibodies (PRA), human leucocyte antigen (HLA) typing, donor-specific antibody detection assays (DSA) and complement-dependent cytotoxicity assays (CDC).

A protocol for ascertaining a donor match was drawn up which included an ABO compatible blood group match and a lymphocyte cross match <20% (preferably <10%). Other criteria that considered were sex, size and colour match and no history of malignancy, infections (HIV, hepatitis C virus, hepatitis B surface antigen or severe deformity of the hand.

Induction and maintenance regime

Induction immunosuppression was by thymoglobulin and the maintenance by the standard triple-drug therapy [Table 1].

Table 1: Immunosuppression regime

Post operative Day	*Immunosuppression*
Day 1	Injection thymoglobulin I.V. at 1.5 mg/kg
	Injection methyl prednisolone I.V. at 500 mg stat
	Capsule tacrolimus 0.05 mg/kg stat
	Tablet mycophenolate mofetil 1000 mg stat
Before vascular clamp release	Injection methyl prednisolone I.V. 500 mg stat
Day 0	Capsule tacrolimus at 0.1 mg/kg in two divided doses (8 am and 8 pm)
	Injection methyl prednisolone I.V. 250 mg stat
	Injection thymoglobulin I.V. at 1.5 mg/kg
	Tablet mycophenolate mofetil 1000 mg twice daily (8 am and 8 pm)
Day 1 onwards (for 5 days)	Injection thymoglobulin I.V. at 1.5 mg/kg × 3 days
	Tablet prednisolone at 0.5 mg/kg/day
	Capsule tacrolimus at 0.1 mg/kg in two divided doses (8 am and 8 pm)
	Tablet mycophenolate mofetil 1000 mg twice daily (8 am and 8 pm)
Maintenance regimen	Tablet prednisolone at 0.5 mg/kg/day
	Capsule tacrolimus dose adjusted according to serum tacrolimus levels
	Tablet mycophenolate mofetil 1000 mg twice daily (8 am and 8 pm)

I.V.: Intravenous

Table 2: Banff criteria

Grade	*Microscopic findings*
Grade 0	None – Rare inflammatory infiltrates
Grade1	Mild – Mild perivascular lymphocytic and eosinophilic infiltrates. No involvement of overlying epidermis
Grade 2	Moderate – Moderate to severe perivascular inflammation with or without mild epidermal and/or adnexal involvement
Grade 3	Severe – Dense inflammation and epidermal involvement with epithelial apoptosis dyskeratosis and/or keratinolysis
Grade 4	Necrotising acute rejection – Necrosis of single keratinocytes and focal dermal-epidermal separation

Monitoring protocol

A monitoring protocol was drawn up where by serial protocol, skin biopsies (using a 4 mm punch) would be carried out weekly for the first 3 months, followed by once in 2 weeks up to the 6 months and then monthly for 1 year. In the eventuality of any suspicious lesions or skin changes, skin biopsy would be taken from the suspicious areas and assessed as per the Banff criteria[1] [Table 2].

Systemic levels of tacrolimus were to be assayed weekly for the first 6 weeks and then every alternate week for the next 6 weeks and then monthly. Tacrolimus assay was also be repeated in the eventuality of suspicion of any rejection episodes. The target tacrolimus level was 5–10 ng/dl.

The presence of any lesions or colour changes or any unexplained swelling was also considered as an indicator of a potential rejection episode necessitating a biopsy.

Immediate postoperative monitoring and care

After the surgery, the patients were cared for in a transplant Intensive Care Unit (ICU) for the first 2 weeks and thereafter in the transplant ward. Standard transplant isolation precautions were followed. The vascularity of the grafts was monitored using separate pulse oximeter for each hand and one on the foot (as a control). Vital signs were monitored daily. Complete blood count was done daily for the 1st week to look for immunosuppression-related cytopenia. Serum creatinine was assessed daily for the 1st week, twice weekly for the next 2 weeks, once a week for the next 2 months and once a month for the next 3 months and then once every 3 months thereafter to watch for drug-induced renal toxicity. Fasting and postprandial blood glucose levels and lipid profile were done every 3 months. Serum tacrolimus levels were checked as per the plan described earlier. Protocol biopsies were taken as described and while suspecting a rejection. This was done by a punch biopsy of 4 mm diameter incorporating all layers of the skin from the dorsal surface of the hand and forearm.

Our first patient developed basal atelectasis of the right lung on the 1st postoperative day. This was managed conservatively. On the second postoperative day, the distal portion of the long ulnar skin flap of the transplanted left hand developed areas of vascular compromise. In the presence of immunosuppression, any necrotic tissue would have had a catastrophic outcome. Immediate debridement of all tissues with doubtful vascularity was performed followed by resurfacing with a free anterolateral thigh flap. To minimise the risk of general anaesthesia, the surgery was performed under regional anaesthesia (combination of supraclavicular block and femoral block). On the 3rd postoperative day, the patient developed pancytopenia induced by antithymocyte globulin used for induction immunosuppressant therapy. Hence, the induction immunosuppressant therapy had to be interrupted and it was finally completed on postoperative day 8. He sustained superficial second-degree burns in the transplanted hand while inadvertently holding a glass of hot tea in his insensate right hand.

The second patient stayed in the ICU for 2 weeks and in the isolation ward for another four weeks. He had an uneventful recovery.

Immunosuppression related issues

Both the transplants were performed between ABO-matched donors and recipients, and the lymphocyte cross match was <10%. PRA and DSA levels were not performed for both the transplants before transplants. Both the transplants were between sexually identical individuals, with a compatible size match. However, there was a colour mismatch in the case of the second transplantation as the recipient was a fair-skinned individual from Afghanistan, and the donor was a dark-skinned south Indian.

Immunosuppression-related complications in the first patient included tinea versicolor on the neck, herpes labialis and paronychia on the right index finger. These were managed medically. He also had transient diabetes mellitus during the pulse steroid therapy and tacrolimus-associated renal dysfunction (mildly elevated serum creatinine) which was tackled by adjusting the dose of tacrolimus. The second patient had no significant issues of similar sorts in the immediate postoperative period.

There were 5 rejection episodes during the 1st-year following the transplant in case of the first transplant and 1 episode in case of the second transplant [Table 3].

The first episode in case of the first transplant was an antibody-mediated rejection which was treated with two doses of rituximab 500 mg each and one dose of immunoglobulin (IgG). The remaining episodes of rejection were treated with pulse steroid therapy with 500 mg of methyl prednisolone and adjustment of the dose of tacrolimus.

The first recipient developed hypertension and was started on antihypertensives. Both the recipients had a few episodes of infections, which were treated with appropriate medication [Table 4].

DISCUSSION

The biggest challenge in case of VCAs is to counter the immune response of the host caused by differences in HLA of recipient and donor. HLAs are integral cell membrane glycoproteins that bind the antigen peptide fragments and present them to the lymphocytes. Their main function is concerned with immunity and self-recognition. Compatibility of the HLA of the donor and the recipient increases the chance of successful transplantation.

Table 3: Rejection episode details of both the recipients

Rejection episode	*Timing*	*Management*	*Tacrolimus level*
Recipient 1			
Antibody-mediated rejection	2 weeks	Rituximab 2×500 mg	4.6
Grade I ACR	4 weeks	Tapering of tacrolimus and oral steroid dosage	7.3
Grade II ACR	4 months	Pulse therapy with methyl prednisolone (500 mg×3)	8.6
Grade III ACR	8 months	Pulse therapy with methyl prednisolone (500 mg×2)	8.3
Grade II ACR	9 months	Tapering of tacrolimus and oral steroid dosage	8.8
Recipient 2			
Grade III ACR	1 month	Pulse therapy with methyl prednisolone (500 mg×3)	8.9

ACR: Acute cellular rejection

Anti-HLA antibodies could form following sensitisation events such as pregnancy, blood or platelet transfusions or previous transplants. If detected, the HLA antibodies could prove detrimental to the graft as it may target the donor tissue, as a part of the immune response. To know, if the recipient has any anti-HLA antibodies, PRA screen is helpful. It detects the presence of anti-HLA IgG antibodies and differentiates it into Class I and Class II types. PRA screening was not done in both these patients.

To know that the recipient has anti-HLA antibodies against a particular donor, DSA test detects the presence of IgG antibodies against donor's HLA antigens, which could target the donor's organ or tissues. There are multiple ways of assessing the compatibility of the donor organ to the recipient.[2] Of these, CDC assay using peripheral blood sample was the method adopted for solid organ transplantation at our institution. This identifies preformed antibodies in the recipient's serum against the donor's cells, which are responsible for rapid and irreversible destruction of the graft upon transplantation. Hence, we adopted the same for both of these transplants.

The results are reported as percentage of cross-reaction between the donor HLA antigens on the lymphocytes and preformed antibodies in the recipient's serum in the presence of complement and a vital dye [Table 5]. DSA estimation done later on these two recipients did not reveal the presence of any.

Triple drug therapy is the mainstay of immunosuppression in most of the centres performing hand transplantations. The Louisville group used a steroid-free regime to avoid the detrimental effects of long-term steroid usage but have failed to provide convincing results.[3] Sirolimus has been substituted in some patients[4] in place of tacrolimus for its superior renal toxicity profile. The Pittsburg group attempted donor bone marrow transplantation at the time of hand transplantation and followed that with tacrolimus monotherapy maintenance.[5] Long-term results of that attempt are yet to be ascertained.

Table 4: Complication(s) profile of both the recipients

Complication and timing	*Management*
Hypertension (2nd month)	Antihypertensives
Loose stools (2nd month)	Stool culture – salmonella Antibiotics
Herpes labialis (6th month)	Acyclovir
Paronychia (7th month)	Antibiotics
Upper respiratory tract infection (8th month)	Sputum culture – sterile Antibiotics
Upper respiratory tract infection (8th month)	Sputum culture – sterile Antibiotics
Patient 2	
Loose stools with weight loss of 12 kg (18 months)	Stool examination – giardia lamblia colonoscopy, OGD scopy and USG-normal

USG: Ultrasonography, OGD: Oesophagogastroduodenoscopy

Table 5: Interpretation of complement dependent cytotoxicity# results

Negative (<10%)-favourable for transplantation
Marginal positive (11%-20%)-prior plasmapheresis indicated
Positive cross reaction (>20%)-unfavourable for transplantation

#Also known as lymphocyte cross-match

The risks associated with the use of long-term immunosuppression are significant. These could be infectious or metabolic or malignancies. Diabetes, hypertension and dyslipidaemia are the most common metabolic side effects that are encountered in these patients. Derangement of renal function on accounts of the usage of calcineurin inhibitors (tacrolimus) is very pertinent with about 16.5% of the recipients facing this at the end of 3 years. Cardiovascular risks are another major potential complication. They are also prone to various malignancies such as lymphomas and non-melanomatous skin cancers. The group at Valencia reported a case of basal cell carcinoma of the ala of the nose, which was successfully resected. Infections can occur commonly with more than 60% of them having an episode at some point in time.

CONCLUSION

A comprehensive plan has to be drawn up for immunological screening, selection and the post-operative

immunosuppressant usage. The ultimate goal of these immunosuppression modalities is to achieve a state of donor-specific tolerance. The ideal regime is yet to be identified with various groups attempting a range of options from lymphoid irradiation to donor bone marrow infusion to costimulatory blockade. Our surgical team was highly facilitated by the renal transplant physician who helped to chalk out and assume responsibility of day-to-day management for immune-related issues. With time and experience, the transplant surgical team also became comfortable and proficient in managing these patients. However, maintain close liaison with the transplant physicians always will make organising a hand transplant programme safer and easier.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cendales LC, Kanitakis J, Schneeberger S, Burns C, Ruiz P, Landin L, *et al*. The Banff 2007 working classification of skin-containing composite tissue allograft pathology. Am J Transplant 2008;8:1396-400.
2. Ashvetiya T, Mundinger GS, Kukuruga D, Bojovic B, Christy MR, Dorafshar AH, *et al*. Donor-recipient human leukocyte antigen matching practices in vascularized composite tissue allotransplantation: A survey of major transplantation centers. Plast Reconstr Surg 2014;134:121-9.
3. Breidenbach WC, Gonzales NR, Kaufman CL, Klapheke M, Tobin GR, Gorantla VS, *et al*. Outcomes of the first 2 American hand transplants at 8 and 6 years posttransplant. J Hand Surg Am 2008;33:1039-47.
4. MacKay BJ, Nacke E, Posner M. Hand transplantation. A review. Bull Hosp Jt Dis 2014;72:76-88.
5. Brandacher G, Gorantla VS, Lee WP. Hand allotransplantation. Semin Plast Surg 2010;24:11-7.