Risk Assessment of Immunosuppressive Therapy in Facial Transplantation

Dalibor Vasilic, M.D.
Rita R. Alloway, Pharm.D., B.C.P.S.
John H. Barker, M.D., Ph.D.
Allen Furr, Ph.D.
Rachael Ashcroft
Joseph C. Banis, Jr., M.D.
Moshe Kon, M.D., Ph.D.
E. Steve Woodle, M.D.

Louisville, Ky.; Cincinnati, Ohio; and Utrecht, The Netherlands

Background: Immunosuppression-related risks are foremost among ethical concerns regarding facial transplantation. However, previous risk estimates are inaccurate and misleading, because they are based on data from studies using different immunosuppression regimens, health status of the transplant recipients, tissue composition, and antigenicity. This review provides a comprehensive risk assessment for facial transplantation based on comparable data of immunosuppression, recipient health status, and composition and antigenicity of the transplanted tissue.

Methods: The risk estimates for face transplantation presented here are based on data reported in clinical kidney (10-year experience) and hand transplantation (5-year experience) studies using tacrolimus/mycophenolate mofetil/corticosteroid therapy. Mitigating factors including ease of rejection diagnosis, rejection reversibility, infection prophylaxis, patient selection, and viral serologic status are taken into account.

Results: Estimated risks include acute rejection (10 to 70 percent incidence), acute rejection reversibility (approximating 100 percent with corticosteroid therapy alone), chronic rejection (<10 percent over 5 years), cytomegalovirus disease (1 to 15 percent), diabetes (5 to 15 percent), hypertension (5 to 10 percent), and renal failure (<5 percent).

Conclusions: A review of these data indicates that previously reported estimates of immunosuppression-related risks are outdated and therefore should no longer be used. These updated risk estimates should be used by facial transplant teams, institutional review boards, and potential recipients when considering the immunologic risks associated with facial transplantation. (*Plast. Reconstr. Surg.* 120: 657, 2007.)

Although facial transplantation has now become a clinical reality,[1,2] there exist considerable differences of opinion regarding the ethics of moving this new treatment into the clinical arena. At the center of this debate is the question, Do the risks posed by the lifelong immunosuppression that recipients will have to take justify the benefits of this new treatment?[3–20]

Critics of facial transplantation base their position on immunologic risk data published in 2004 by the Royal College of Surgeons' "Facial Transplantation: A Working Party Report from the Royal College of Surgeons of England," which states that "It is not possible to accurately predict the likelihood of immunological rejection after facial transplantation, but a graft loss of around 10 percent from acute rejection within the first year and significant loss of graft function from chronic rejection in around 30–50 percent of patients over the first 2–5 years might be a reasonable estimate."[21] These projections have had a great influence on framing the risk-versus-benefit debate in face transplantation,[7,11,16,17,22] and indeed have even influenced the position statements published by influential bodies representing plastic surgeons, such as the French National Consultative Ethics Committee,[26] the American Society of Plastic Surgeons, and the American Society of Reconstructive Microsurgery.[23] Despite the great importance attached to these projections,

From the Departments of Surgery and Sociology, University of Louisville; Division of Nephrology, Department of Internal Medicine, and Division of Transplantation, Department of Surgery, University of Cincinnati; and Department of Plastic, Reconstructive, and Hand Surgery, University of Utrecht.
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we contend that they are inaccurate and therefore misleading.[6,24,25] We base this statement on three important facts:

1. The studies on which these estimates were based were performed using immunosuppression regimens other than those that will be and are being used in facial transplantation.
2. The health status of the solid organ transplant recipients in these studies was significantly different from that of face transplant recipients.
3. The tissue composition and antigenicity of solid organs (reported in these studies) is very different from that of facial tissues.

DIFFERENT IMMUNOSUPPRESSION REGIMENS

Although solid organ transplant studies can be used to accurately estimate risk data for face transplantation, the studies chosen must use the same drug regimens as those that will be and are being used in facial transplantation (tacrolimus/mycophenolate mofetil/corticosteroids). The above-referenced report estimated 10 percent graft loss in the first year and 30 to 50 percent chronic rejection in the first 2 to 5 years,[21] when in fact, based on human hand transplant data, since 1998 there has been 0 percent graft loss at 1 year and 0 percent chronic rejection at 2 years after transplantation.[28] Substantial data exist regarding immunosuppression-related risks in kidney transplant recipients receiving tacrolimus, mycophenolate mofetil, and corticosteroids at doses similar to those used in human hand and face transplantation (tacrolimus, 3 to 13 ng/ml initial 12-hour trough level; mycophenolate mofetil, 0.5 to 2 g/day; and corticosteroids, 2.5 to 15 mg/day maintenance dose).[28-43] Combined and analyzed, these data can provide a better informed approximation of the immunosuppression-associated risks of facial transplantation than was previously published.

HEALTH STATUS

The physical and psychological health status of face and solid organ transplant recipients varies significantly. Evaluation of immunosuppression-associated risks must be interpreted in the context of preexisting comorbidities in individual populations. For example, kidney transplant recipients possess significant pretransplant comorbidities that include hypertension, diabetes, anemia, bone disease, hyperlipidemia, systemic calcification, accelerated atherosclerosis, and neuropathy. In contrast, facial transplant recipients will likely have substantially less comorbidity. Accurate risk data can be derived from human hand transplant experience, in which case the health status of hand and facial tissue recipients would be similar.

TISSUE COMPOSITION AND ANTIGENICITY

The composition and antigenicity of facial tissues differs from solid organs. Accurate risk data for facial transplantation can be derived from human hand transplant experience, in which case the composition and antigenicity of the transplanted tissues (e.g., skin, muscle) are similar. In contrast to the above-cited Royal College of Surgeons report, clinical experience in hand transplantation indicates an unusually high occurrence of acute rejection episodes compared with human kidney transplantation.[28] This is most likely attributable to the high antigenicity of skin.

For this analysis and for the sake of clarity, immunosuppression-associated risks are divided into two groups: immunologic and nonimmunologic. Immunologic-related risks include underimmunosuppression (acute and chronic rejection) and overimmunosuppression (opportunistic infections and malignancies). Nonimmunologic risks are primarily drug-related toxicities (cardiovascular, renal, gastrointestinal, and bone toxicities; diabetes; and noncompliance). Contrary to previously published risk data, this review focuses on recent reports from studies of kidney (10-year experience) and hand (5-year experience) transplantation that used tacrolimus/mycophenolate mofetil/corticosteroid maintenance therapy. On the basis of these data, we provide a more accurate estimate of how these risks will apply in facial transplantation.

IMMUNOLOGIC RISKS

Optimal immunosuppression, infection prophylaxis, and medical management of transplant recipients results in effective prevention of acute and chronic rejection, infection, cancer, cardiovascular risk, and drug-related toxicities. Achieving a balance between overimmunosuppression and underimmunosuppression requires an appreciation of other factors, including nutritional status, preexisting disease, age, pretransplant morbidity (e.g., diabetes mellitus, hypertension), and posttransplant immunomodulating viral infections (e.g., cytomegalovirus, Ebstein-Barr virus, and other herpes viruses). Balanced immunosuppression therefore, is most effectively attained by a multidisciplinary approach, where experience from solid organ and composite tissue allotrans-

plantation are both taken into consideration to manage immunosuppression.

Underimmunosuppression

Acute Rejection

Acute rejection and allograft loss rates in kidney transplantation have decreased with advances in immunosuppression. The introduction of tacrolimus in 1992 allowed a decrease in 1-year acute rejection rates from the previous 50 percent with cyclosporine-based immunosuppression to approximately 30 percent.[29] Similarly, the introduction of mycophenolate mofetil in 1995 resulted in acute rejection rates of 30 percent when used concomitantly with cyclosporine.[30] Subsequent studies with combined tacrolimus/mycophenolate mofetil/corticosteroid regimen provided 1-year acute rejection rates below 20 percent[31–43] (Table 1).

Using the tacrolimus/mycophenolate mofetil/corticosteroid regimen, acute rejection rates in hand transplant recipients was recently reported to be 67 percent at 1 year (excluding one transplant between identical twins; 12 of 18 patients experienced 26 rejection episodes). These higher acute rejection rates in hand transplants (compared with kidney transplants) may be explained in part by the greater immunogenicity of skin tissue.[45–49] In these cases, antithymocyte globulin, basiliximab, and no induction protocols were used in 11, five, and two patients, respectively, and maintenance therapy consisted of tacrolimus/mycophenolate mofetil/corticosteroid in 15 patients, rapamycin/mycophenolate mofetil in one patient, rapamycin in one patient, and topical tacrolimus and steroids in one patient[28] (Table 1). We included all 18 of these cases in our risk evaluation because of a lack of published data, making a distinction between the risk profiles in tacrolimus/mycophenolate mofetil/corticosteroid and the other maintenance therapies in hand transplantation.

All acute rejection episodes were successfully reversed regardless of the antirejection therapy used. Acute rejection episodes were treated with tacrolimus and/or corticosteroids, with or without topical corticosteroid ointment. In five of the 12 first acute rejection episodes, 42 percent were treated with systemic corticosteroid therapy. Recurrent acute rejection episodes were treated with topical tacrolimus or topical corticosteroids [two of 14 episodes (14.3 percent)] or in conjunction with systemic corticosteroids [five of 14 rejection episodes (35.7 percent)]. Eighteen percent of patients received T-cell–depleting antibody therapy, antithymocyte globulin antithymocyte globulin [two of 18 patients (11.1 percent)], or Campath-1H[44] [one of 18 patients (5.6 percent)], whereas 19.2 percent of cases (five of 26 rejection episodes) were treated with basiliximab.

Allograft and patient survival were 100 percent at 24 months, and at a mean follow-up of 43 months, allograft and patient survival were 89 percent and 100 percent, respectively.[28] Two graft failures were reported, one attributable to medication noncompliance[45] and another to unclear cause[27,28] (Table 1). These high allograft survival rates in hand transplant recipients (despite relatively high acute rejection rates) may be attributable to early recognition of acute rejection by visual inspection of the skin. Acute rejection in hand allotransplants is manifested by early, visually apparent, cutaneous[44,46,49] tissue changes that have a high correlation with histopathologic findings (Table 2). Combined, visual inspection and skin biopsies provide an easy means for monitoring and prompt diagnosis of acute rejection.

The importance of early diagnosis of acute rejection has been demonstrated in the extensive experience with kidney transplantation. Current surveillance methods for acute rejection in solid organ transplants are relatively insensitive (Table 2), because of the mostly silent clinical manifestations, which often result in delayed antirejection treatment and decreased long-term allograft survival. The significance of early diagnosis and treatment of acute rejection has been illustrated by prospective studies of protocol renal allograft biopsies,[50,51] where unrecognized acute rejection was associated with an increased risk of chronic allograft nephropathy and late graft loss.[50,52]

Extrapolation of these data to facial transplantation indicates that the incidence of acute rejection may range between 10 and 70 percent. It is reasonable to expect that most acute rejection episodes will be diagnosed early, enabling immediate dosing adjustment in maintenance immunosuppressive agents and/or topical therapy, resulting in high reversal rates. Contrary to the 10 percent failure rate predicted in the Royal College of Surgeons' report for human facial transplants,[21] these data indicate that risk of allograft loss will be minimal.

An additional risk factor that needs to be taken into consideration in face transplant recipients is related to sensitization to human leukocyte antigens. Patients with facial disfigurement caused by severe trauma or extensive burns may have previously received human skin allograft and/or blood transfusions. Although whether acute rejection risk is associated with human leukocyte antigen

Table 1. Rejection and Graft Survival Rates in Renal and Hand Transplant Recipients Receiving Tacrolimus, Mycophenolate Mofetil, and Corticosteroids as Maintenance Therapy

Study	No. of Patients on Tacrolimus/MMF/ Corticosteroid Maintenance	Follow-Up (yr)	AR: Biopsy Proven (%)	AR: Steroid Resistant (%)	AR Associated Graft Failure (%)	CR (%)	CR Associated Graft Failure (%)	Graft Survival (corrected for death with functioning graft) (%)	Publication Date
Kidney (SOT)									
Johnson et al.[33]	72	1	15.3	4.2	NR	NR	NR	89*	2000
Ahsan et al.[34]	72	2	16.7	5.6	NR	NR	NR	82.8*	2001
Gonwa et al.[35]	72	3	17	5.6	NR	NR	NR	80.6*	2003
Miller et al.[36]	117	0.5	18	NR					2000
		1	20.5	7.7	0	0	0	99.2	
Woodle et al.[37]	195	1	6.2	NR	0	NR	NR	100	2005
Gonwa et al.[38]	176	0.5	11.4	NR	<2	NR	NR	97.8	2003
Mendez et al.[39]	176	1	13	NR	NR	<2.8	NR	97.2	2005
Ciancio et al.[40]	458	0.5	4.6	NR	NR	NR	NR		2002
		1	7.9	NR	0.4	NR	0.4	97	
Ciancio et al.[41]	50	0.5	2	NR	0	NR	NR		2004
		1	4	NR	0	NR	0	98	
Vanrenterg et al.[42]	277	0.5	17	6.5	NR	NR	NR	94.2	2005
Rostaing et al.[43]	278	0.5	16.5	4.3	0.7	NR	NR	95.7	2005
Ciancio et al.[44]	60	0.5	13.4	NR		NR	NR		2005
		1	16.7	NR	0	NR	NR	98.3	
Ciancio et al.[45]	305	0.5	2.3	NR	NR	NR	NR	96	2003
		2.25	5	NR	NR	NR	NR		
Hand (CTA)									
Lanzetta et al.[28]	15†	2	67‡	3.9§	0	0	0	100	2005
Lanzetta et al.[28]	15†	2.5–6.5				5.6‖	5.6‖	89¶	

MMR, mycophenolate mofetil; AR, acute rejection; CR, chronic rejection; NR, not reported; SOT, solid organ transplantation; CTA, composite tissue allotransplantation.

*Reported graft survival was not corrected for death with functioning graft because of a lack of data.

†Fifteen of 18 patients received tacrolimus/mycophenolate mofetil/corticosteroid maintenance therapy and three patients received rapamycin/mycophenolate mofetil/rapamycin alone and topical tacrolimus/corticosteroid therapy.

‡Percentage presented includes 12 of 18 allotransplants, excluding one transplant between identical twins.

§Some of the recurrent acute rejection episodes were treated with antibody therapy, but only one of 18 cases has been documented as steroid-resistant acute rejection.[46]

‖Percentage presented includes one of 18 allotransplants, excluding one transplant between identical twins (it must be noted that one additional transplant was lost as a result of unclear cause.[27,28]

¶Two reported graft failures (two of 18), one because of noncompliance and one because of unclear cause.

Table 2. Comparison of Rejection Markers in Solid Organ Transplantation and Composite Tissue Allotransplantation

	A		B		C	
Marker	Specificity	Sensitivity	Daily Accessibility	Periodic Accessibility (monthly)	Associated Monitoring Morbidity	Associated Monitoring Costs
Kidney (SOT)						
Serum creatinine	–	–	–	+++	–	+/–
Calculated renal clearance	–	–	–	+++	–	+/–
Measured renal clearance	+/–	+/–	–	+/–	+/–	+/–
Renal biopsy	+++	+++	–	–	++	+++
Other/experimental biomarkers	Und.	Und.	Und.	Und.	–	++
Face transplant (CTA)						
Visual inspection	++	++	+++	+++	–	–
Skin biopsy	+++	+++	–	+	–	++

Und., undetermined and not a part of contemporary standard clinical care; SOT, solid organ transplantation; CTA, composite tissue allotransplantation.
A: +++, accepted standard; ++, high; +/–, moderate;–, low;–, very low/poor. B: +++, excellent; ++, very good; +/–, moderate;–, difficult;–, very difficult/impossible. C: +++, high; ++, appreciable/high; +/–, moderate;–, low;–, very low/nonexistent.

sensitization in facial transplantation is not known, these patients may have significant degrees of human leukocyte antigen sensitization. Panel reactive antibody testing and additional pretransplant immunologic monitoring (human leukocyte antigen typing and T- and B-cell crossmatching) will be essential in the initial phases of facial transplantation to adequately assess sensitization and its risk.

Chronic Rejection

The exact mechanisms of chronic rejection have not been defined; however, both immunologic and nonimmunologic factors have been implicated.[53] Immunologic factors that influence chronic rejection in transplanted kidneys include acute rejection, human leukocyte antigen sensitization, human leukocyte antigen matching, and noncompliance. Nonimmunologic factors include diabetes, hypertension, ischemia/reperfusion injury, donor age, calcineurin inhibitor nephrotoxicity, lipid abnormalities, and cytomegalovirus infection. Discriminating between individual contributions of immunologic and nonimmunologic factors in the cause of chronic rejection continues to pose a substantial challenge in clinical studies.

In humans, a few studies have reported the role of acute rejection in the specific tissue components of composite tissue allotransplantation, but not in chronic rejection. In one report, rectus abdominis and external oblique muscle allografts were transplanted for reconstruction of a scalp defect following resection of a cutaneous squamous cell carcinoma. An early acute rejection episode was successfully reversed and subsequent biopsy specimens in the first posttransplant year demonstrated mild rejection without signs of graft failure.[54] In another report, synchronous transplantation of a kidney and small split-thickness skin graft in six patients resulted in long-term skin allograft survival up to 7 years.[55] Neither of these studies described or reported chronic rejection.

In one of 18 human hand transplants performed, clinical and histologic characterization of what was believed to be chronic (cutaneous) rejection was based on findings in a patient whose graft failed because of medication noncompliance.[45] Examination of the rejected allograft demonstrated a histologic picture identical to chronic lichenoid graft-versus-host disease.[45,56] In the remaining 17 patients, chronic rejection has not been reported at a median follow-up of 43 months (Table 1).

These low chronic rejection rates in human hand allotransplantation may be attributable to several factors. First, follow-up is relatively short. Second, risk factors for chronic rejection in kidney transplantation (e.g., hypertension, hyperlipidemia) are less common in hand transplant recipients. Similarly, composite tissue allotransplantations do not appear to be subject to vascular and parenchymal toxicity of immunosuppressive medication, as are kidney allografts. Finally, early recognition enabling early treatment and reversal of acute rejection may play an important role in

minimizing chronic rejection in composite tissue allotransplantation.

Chronic rejection rates in human hand transplants are considerably lower than the 30 to 50 percent figures predicted for human face transplants in the report by the Royal College of Surgeons.[21] The low incidence of chronic rejection, even with concomitant high acute rejection rates,[28] suggests that chronic rejection may not be as great a threat in hand and therefore in facial transplantation.

Overimmunosuppression

There are currently no objective means for evaluating the overall state of immunosuppression. As a result, clinical manifestations of underimmunosuppression (acute rejection) and overimmunosuppression (infection and malignancy) provide only the indicators of the general degree of immunosuppression.

Infection

Overimmunosuppression leading to opportunistic infections usually include *Pneumocystis carinii* pneumonia, viral disease (e.g., cytomegalovirus, Epstein-Barr virus), and fungal infections.[57] Over the past decade, improved selectivity of immunosuppressive regimens; the availability of new antiviral, antibacterial, and antifungal agents; and improvements in diagnostic tests have allowed earlier and more accurate diagnosis and reduced the incidence and severity of posttransplant infections.[57,58]

Bacterial Infections

Most bacterial infections in transplant recipients occur in the early posttransplant period, and are related more to the surgical procedure than to overimmunosuppression.[59] A small minority of transplant patients with bacterial infection may develop a life-threatening sepsis; however, most bacterial infections are readily treatable and are not associated with substantial morbidity.[57]

In renal transplant recipients, the tacrolimus/mycophenolate mofetil/corticosteroid regimen has been associated with serious bacterial infection rates between 5 and 20 percent, with a mortality rate between 0.5 and 4 percent.[31,34–36,38,39,42,43] In human hand transplants, the overall bacterial infection rate has been reported to be 11 percent (two infections, *Clostridium difficile* enteritis and *Staphylococcus aureus* osteitis), with no reported deaths or resulting allograft loss.[28]

Fungal and Protozoal Infections

Tacrolimus/mycophenolate mofetil/corticosteroid regimen–associated fungal infections in renal transplant recipients leads to hospitalization rates ranging from 0.5 to 11 percent in the first posttransplant year[31,34–36,38,39,42,43] (Table 3). In human hand transplant recipients, fungal infections (all cutaneous mycoses without invasive disease) occurred in 28 percent of cases, with no patient death or allograft loss.[28] The same fungal infection risks should be expected in face transplantation.

Viral Infections

Historically, viruses have posed the greatest infectious threat to transplant recipients, with cytomegalovirus being the most important pathogen.[57,60] Cytomegalovirus infection may present as tissue invasive disease causing pneumonia, pancreatitis, hepatitis, enteritis, or retinitis. Cytomegalovirus infection rates in renal transplant recipients receiving tacrolimus/mycophenolate mofetil/corticosteroids (requiring hospitalization) ranged from 2 and 14 percent, whereas Epstein-Barr virus infection rates ranged from 0 to 3 percent.[31,34–36,38,39,42,43] The viral infection rate in hand transplant recipients was reported to be 34 percent.[28] Of these, cytomegalovirus viral infections accounted for 28 percent, of which 11 percent of patients developed cytomegalovirus invasive disease. Only 6 percent of patients experienced cutaneous herpes simplex infections. Although viral infections have not caused patient death or allograft loss,[28] a correlation was observed between cytomegalovirus invasive disease and acute rejection.[61] The same viral infection risks should be expected in face transplantation.

Posttransplant Malignancies

Posttransplant Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder is a serious and potentially fatal complication affecting solid organ transplant recipients, with incidences of 1 percent in kidney and 9 percent in heart and lung transplantation.[62,63] Posttransplant lymphoproliferative disorder includes a wide spectrum of disorders, ranging from benign hyperplasia to malignant lymphomas,[64] with pathogenesis related to two factors: B-cell proliferation induced by Epstein-Barr virus infection[61–63,65–67] and the net state of immunosupression.[68] Posttransplant lymphoproliferative disorder occurs most often within the first posttransplant year, with a decrease in risk thereafter,[69] and although the prognosis varies with the extent of disease, overall survival rates are approximately 50 percent. In prospective studies of tacrolimus/mycophenolate mofetil/corticosteroid therapy in kidney transplant recipients,

Table 3. Infection Rates in Renal and Hand Transplant Recipients Requiring Hospitalization under Tacrolimus/Mycophenolate Mofetil/Corticosteroid Therapy

Study	No. of Patients	Follow-Up (yr)	Total Infection (%)	Infection Death (%)	Bacterial Infection Total (%)	Bacterial Infection Death (%)	Fungal Infection Total (%)	*Candida* (%)	*Aspergillus* (%)	PCP (%)	Viral Infection Total (%)	CMV Viremia (%)	CMV Disease (%)	HSV (%)	EBV (%)	Other (%)†	Publication Date
Kidney (SOT)																	
Johnson et al.[33]	72	0.5	NR	2.7	NR	2.7	11.1	8.3	1.4	0	13.9	9.7	4.2	2.8	2.8	5.6	2000
Miller et al.[36]‡	117	1	24.5*	2.6	NR	NR	18*	14.5*	1.7*	0	NR	5.1*	1.7	NR	NR	1.7*	2000
Ciancio et al.[41]	50	1	22	4*	16	4	NR	NR	NR	NR	6	2	2	NR	0	4	2004
Gonwa et al.[38]	176	0.5	NR	NR	NR	NR	4.5	4.5	0	NR	12	5.1	2.3	2.3	NR	2.3	2003
Ciancio et al.[40]	458	1	11.6	2.2	5.7	NR	0.4	NR	NR	NR	5.4	1.3	1.5	NR	NR	2.6	2002
Woodle et al.[37]*	195	1	30.8*	0A	NR	0*	6.1*	NR	NR	NR	NR	<10.2*	<10.2*	NR	NR	NR	2005
Ciancio et al.[44]	60	1.25	16.7	1.7	15	1.7	NR	NR	NR	NR	NR	<1.7	<1.7	NR	NR	NR	2005
Ciancio et al.[45]	305	2.25	8.52	0.35	5	0.35	NR	NR	NR	NR	3.6	1.7	1	0.7	NR	1.7	2003
Hand (CTA)*																	
Lanzetta et al.[28]	18	2.5–6.5	73*	0	11	0	28*‡	0	0	0	33.5*	16.7*	11.1*	5.5*	NR	NR	2005

SOT, solid organ transplant; CTA, composite tissue allotransplant; NR, not reported; PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus.

*Infectious complications reported in this study include infections with and without required hospitalization.

†Other infections include viral infections such as hepatitis B and C and nonspecified infections.

‡All fungal infections in hand transplant recipients remained limited to cutaneous mycosis.

the incidence of posttransplant lymphoproliferative disorder was 1.4 percent at 6 months[31] and 3 years[70] in one study and 0.5 percent at 1 year in a second study.[35] Posttransplant lymphoproliferative disorder has not been reported to date in human hand transplant recipients.[28] These considerations indicate that posttransplant lymphoproliferative disorder should occur in less than 1 percent of face transplant recipients.

Kaposi's Sarcoma

Transplantation-associated Kaposi's sarcoma has been linked to human herpesvirus-8[71] and usually presents in the first posttransplant year.[72] The reported 5-year survival rate is approximately 70 percent,[70] and treatment usually consists of immunosuppression reduction, sometimes in combination with irradiation and surgery. In studies with tacrolimus/mycophenolate mofetil/corticosteroid maintenance therapy, Kaposi's sarcoma did not occur within a 3-year follow-up period,[36,37,69] nor has it been reported to date in human hand transplantation.[28]

Skin Cancers

Skin and lip cancers are the most common type of de novo cancer in solid organ transplant recipients, accounting for 50 percent of all malignancies, with a 3-year cumulative incidence of 7.5 percent.[73] In a study describing a 20-year posttransplant follow-up in Australia and New Zealand, skin cancer occurred in 82 percent of kidney transplant recipients.[74] Most skin malignancies can be easily detected and successfully treated by surgical excision, and immunosuppression reduction has been shown to have great therapeutic value in treating aggressive squamous cell carcinoma.[75] Recent renal transplant experiences with tacrolimus/mycophenolate mofetil/corticosteroid therapy have reported squamous cell carcinoma incidences between 0.6 percent at 1 year[37] and 2.8 percent at 3 years.[70] There were no cases of de novo melanoma reported.[37,70] To date, skin cancer has not been reported in human hand transplant recipients at a median follow-up of 43 months.[28] The same risk of skin cancer should be expected in face transplantation.

NONIMMUNOLOGIC RISKS

Nonimmunologic risks are primarily attributable to adverse effects of immunosuppressive and prophylactic agents used in transplant recipients. At present, the greatest risk for graft loss in renal transplant recipients is cardiac-related death with a functioning graft.[76] Immunosuppressive agents may increase cardiovascular risk by affecting cholesterol levels, triglycerides, blood pressure, posttransplant diabetes mellitus, and renal dysfunction. Tacrolimus can exacerbate hypertension by inducing vasoconstriction.[77] Mycophenolate mofetil is virtually devoid of cardiovascular-related adverse effects. Corticosteroids increase the risk of posttransplant diabetes mellitus by increasing insulin resistance[78] and induce hyperlipidemia by interacting with key enzymes in the hepatic lipid synthesis cycle.[79]

Hypertension

The combination of tacrolimus and mycophenolate mofetil has a favorable profile on hypertension compared with other regimens, as hypertension improves following tacrolimus conversion.[80] Interestingly, tacrolimus did not show any effect on blood pressure when administered to healthy individuals.[81] Mycophenolate mofetil has no known effect on blood pressure.[30] Hypertension has not been reported as an immunosuppression-associated adverse effect in human hand transplant recipients,[28] and the same can be expected in face transplant recipients.

Nephrotoxicity

Tacrolimus exerts negative effects on renal function. Vasoconstriction of preglomerular arterioles acutely reduces glomerular filtration, whereas long-term exposure may result in interstitial fibrosis and tubular atrophy.[82] Because of combined immunologic and nonimmunologic effects on the transplanted kidney, the risk of nephrotoxicity in face transplantation can best be estimated by assessing renal outcomes in extrarenal transplantation. In human hand transplant recipients, an increase in creatinine levels was reported in 11 percent of the patients with an absence of renal failure at a median follow-up of 43 months.[28]

Posttransplant Diabetes Mellitus

Posttransplant diabetes mellitus adversely affects patient and graft survival in kidney transplantation.[83] Tacrolimus and corticosteroids increase posttransplant diabetes mellitus risk.[41,83,84] In human hand transplant recipients, posttransplant diabetes mellitus has not been observed, but transient hyperglycemia occurred in 50 percent of the patients, primarily while receiving high corticosteroid doses early after transplantation.[28,85] On the basis of these data, the risk of posttransplant

diabetes mellitus in facial transplantation will likely be low (1 to 5 percent).

Gastrointestinal Adverse Effects

Gastrointestinal effects of tacrolimus and mycophenolate mofetil include nausea, vomiting, and abdominal pain, and more serious effects such as ulceration, gastrointestinal hemorrhage, and intestinal perforation.[30,40,86] In recent renal transplant prospective randomized trials with tacrolimus/mycophenolate mofetil/corticosteroids, the incidence of gastrointestinal effects was 42 percent at 1 year.[87] In human hand transplantation, serious gastrointestinal adverse effects have not been reported. It is reasonable to expect that gastrointestinal adverse effects in facial transplant recipients will be mild and transient. Mycophenolate mofetil coadministration with food, proton-pump inhibitors, antimotility agents, and alternative dosing strategies should minimize gastrointestinal effects.

Posttransplant Bone Disease

Posttransplant bone loss may be induced or exacerbated by immunosuppressive agents in organ transplantation.[88] Corticosteroids suppress osteoblastic function, reduce serum osteocalcin, and induce low-turnover osteopenia and osteoporosis in trabecular bone.[89] Reduction in bone mineral density loss has been demonstrated in early corticosteroid withdrawal studies.[90] Tacrolimus also induces adverse effects on bone metabolism.[91] Mycophenolate mofetil does not influence bone metabolism. In hand transplantation, a single case of avascular necrosis of the hip has been reported, giving a 5.6 percent overall risk.[28] Risks of posttransplant bone disease in facial transplantation will likely be similar to those in hand transplantation.

Noncompliance

The incidence of noncompliance in adult renal transplant recipients ranges from 4.7 (when assessed in relation to graft loss)[64] to 49 percent (when assessed in the absence of rejection episode or graft loss).[92] Factors that influence noncompliance include demographics, psychosocial factors,[92] adverse effects,[93] and complexity of drug regimens.[94] The number of alterations in physical appearance (hirsutism and gingival hyperplasia), particularly noncompliance related, is significantly lower in tacrolimus-based immunosuppression.[29,95] In hand transplantation, noncompliance was reported in one of 18 patients (5.6 percent)[28,45];

Table 4. Summary of Immunosuppression-Related Risks in Kidney (SOT) and Hand (CTA), with Estimated Risks for Facial Transplantation under Tacrolimus/MMF/Corticosteroid Therapy

Complication	Kidney Transplant (%)	Hand Transplant (%)	Face Transplant (%)
Underimmunosuppression			
Acute rejection	10–20	70	10–70
Acute rejection-associated graft failure	<2	0	<2
Chronic rejection	30–80	6*	<10†
Chronic rejection-associated graft failure	30–50	6*	<10†
Overimmunosuppression			
Infection			
Bacterial	5–20	12	5–15
Fungal	5–20	28‡	10–20
PCP	<1	0	<1
Viral	5–20	34	5–30‡
CMV	1–15	28‡	1–20‡
EBV	<5	NR	<5‡
Malignancy			
PTLD	<1	0	<1
Skin cancer	10–50	0	10–50
Drug toxicities			
Hypertension	5–10	NR	5
Dyslipidemia	10–30	NR	5
PTDM	5–15	0	1–3
GI effects	20–40	NR	20–40
Nephrotoxicity as ESRD	3–15	0	0–5

SOT, solid organ transplantation; CTA, composite tissue allotransplantation; NR, not reported; PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder; PTDM, posttransplant diabetes mellitus; GI, gastrointestinal; ESRD, end-stage renal disease.

*Reported percentage of chronic rejection as a consequence of documented noncompliance in one case.

†Estimated chronic rejection rate and associated failure may even be lower, as in hand transplantation only; one case of chronic rejection was attributable to noncompliance.

‡Viral infection rate is highly dependent on donor/recipient serologic status mismatch.

however, careful screening with thorough psychosocial evaluation could have excluded this patient as a candidate and prevented this failure.

Soon after reporting the first face transplant in Amiens, France, newspaper stories reported that the patient had a history of psychiatric problems and had resumed smoking shortly after the procedure, which may endanger blood flow to the transplant.[96] It would be inappropriate to evaluate this case based on nonscientific accounts. However, as in the first hand transplant, this case underscores the importance of careful psychosocial evaluation in the patient screening process. The psychological dimensions in face transplantation will very likely be even more important than they are in hand transplantation. The hopes, anxieties, and stability of all transplant recipients have always precipitated ethical concerns. In the case of facial transplantation, however, the psychological and social dimensions loom much larger because a person's self-image, social acceptability, and sense of normalcy as he or she subjectively experiences them are at stake to a greater degree.[24,25,97]

CONCLUSIONS

When estimating the risks of graft loss, acute and chronic rejection, and drug toxicity in face transplant recipients, it is important to compare "apples with apples," examining risks associated with the same drug regimens, preexisting comorbidities in individual populations, and comparable tissue composition and antigenicity. This article contends that the immunologic risks of face transplantation, though real, are currently less than previously reported and are therefore misleading.

In this article, we provide relevant risk data from large solid organ studies and human hand transplantation. On the basis of these data, we provide more accurate estimations/extrapolations of rejection and complication rates for facial transplants (Table 4). These data present a comprehensive knowledge base for estimating immunosuppression-associated risks and thus provide a solid foundation for patients, physicians, institutional review boards, and professional and lay communities to discuss and make risk-versus-benefit decisions regarding facial transplantation.

John H. Barker, M.D., Ph.D.
Department of Surgery
Plastic Surgery Research
University of Louisville
511 South Floyd Street
320 MDR Building
Louisville, Ky. 40202
jhbark01@louisville.edu

DISCLOSURE

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REFERENCES

1. Devauchelle, B., Badet, L., Lengele, B., et al. First human face allograft: Early report. *Lancet* 368: 203, 2006.
2. China's 1st face transplant successful. Available at: http://news.xinhuanet.com/english/2006-04/14/content_4425653.htm. Accessed April 15, 2006.
3. Wiggins, O. P., Barker, J. H., Martinez, S., et al. On the ethics of facial transplantation research. *Am. J. Bioeth.* 4: 1, 2004.
4. Agich, G. J., and Siemionow, M. Facing the ethical questions in facial transplantation. *Am. J. Bioeth.* 4: 25, 2004.
5. Ankeny, R. A., and Kerridge, I. On not taking objective risk assessments at face value. *Am. J. Bioeth.* 4: 35, 2004.
6. Banis, J. C., Barker, J. H., Cunningham, M., et al. Response to selected commentaries on the AJOB target article "On the ethics of facial transplantation research." *Am. J. Bioeth.* 4: W23, 2004.
7. Baylis, F. A face is not just like a hand: Pace Barker. *Am. J. Bioeth.* 4: 30, 2004.
8. Butler, P. E., Clarke, A., and Ashcroft, R. E. Face transplantation: When and for whom? *Am. J. Bioeth.* 4: 16, 2004.
9. Caplan, A. Facing ourselves. *Am. J. Bioeth.* 4: 18, 2004.
10. Chambers, T. How to do things with AJOB: The case of facial transplantation. *Am. J. Bioeth.* 4: 20, 2004.
11. Maschke, K. J., and Trump, E. Facial transplantation research: a need for additional deliberation. *Am. J. Bioeth.* 4: 33, 2004.
12. Miles, S. H. Medical ethicists, human curiosities, and the new media midway. *Am. J. Bioeth.* 4: 39, 2004.
13. Morreim, E. H. About face: Downplaying the role of the press in facial transplantation research. *Am. J. Bioeth.* 4: 27, 2004.
14. Petit, F., Paraskevas, A., and Lantieri, L. A surgeons' perspective on the ethics of face transplantation. *Am. J. Bioeth.* 4: 14, 2004.
15. Robertson, J. A.. Face transplants: Enriching the debate. *Am. J. Bioeth.* 4: 32, 2004.
16. Rumsey, N. Psychological aspects of face transplantation: Read the small print carefully. *Am. J. Bioeth.* 4: 22, 2004.
17. Strong, C. Should we be putting a good face on facial transplantation? *Am. J. Bioeth.* 4: 13, 2004.
18. Trachtman, H. Facing the truth: A response to "On the ethics of facial transplantation research" by Wiggins. *Am. J. Bioeth.* 4: W33, 2004.
19. Clark, P. A. Face transplantation: Part II. An ethical perspective. *Med. Sci. Monit.* 11: RA41, 2005.
20. Powell, T. Face transplant: Real and imagined ethical challenges. *J. Law Med. Ethics* 34: 111, 2006.
21. Morris, P. J., Bradley, J. A., Doyal, L., et al. Facial transplantation: A working party report from the Royal College of Surgeons of England. *Transplantation* 77: 330, 2004.
22. Rohrich, R. J., Longaker, M. T., and Cunningham, B. On the ethics of composite tissue allotransplantation (facial transplantation). *Plast. Reconstr. Surg.* 117: 2071, 2006.
23. The American Society for Reconstructive Microsurgery (ASRM) and the American Society of Plastic Surgeons (ASPS). Facial Transplantation: ASRM/ASPS Guiding Principles. Available at: http://www.microsurg.org/ftGuidelines.pdf. Accessed June 20, 2006.

24. Brown, C. S., Gander, B., and Cunningham, M. Ethical considerations in face transplantation. *Int. J. Surg.* (Epub 2006 Sept. 5).
25. Gander, B., Brown, C. S., and Vasilic, D. Hand and face transplantation: A new frontier. *Transplant. Int.* 19: 868, 2006.
26. Comit´e Consultatif National d'Ethique pour les sciences de la vie et de la sant´e., L'allotransplantation de tissu composite (ATC) au niveau de la face (Greffe totale ou partielle d'un visage). Available at: http://www.ccne_ethique.fr/english/avis/a_082.htm. *Opinion* 82: 1, 2004.
27. Hettiaratchy, S., Randolph, M. A., Petit, F., et al. Composite tissue allotransplantation: A new era in plastic surgery? *Br. J. Plast. Surg.* 57: 381, 2004.
28. Lanzetta, M., Petruzzo, P., Margreiter, R., et al. The International Registry on Hand and Composite Tissue Transplantation. *Transplantation* 79: 1210, 2005.
29. Pirsch, J. D., Miller, J., Deierhoi, M. H., et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation: FK506 Kidney Transplant Study Group. *Transplantation* 63: 977, 1997.
30. Sollinger, H. W. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients: U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation* 60: 225, 1995.
31. Johnson, C., Ahsan, N., Gonwa, T., et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 69: 834, 2000.
32. Ahsan, N., Johnson, C., Gonwa, T., et al. Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: Results at 2 years. *Transplantation* 72: 245, 2001.
33. Gonwa, T., Johnson, C., Ahsan, N., et al. Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: Results at three years. *Transplantation* 75: 2048, 2003.
34. Miller, J., Mendez, R., Pirsch, J. D., et al. Safety and efficacy of tacrolimus in combination with mycophenolate mofetil (MMF) in cadaveric renal transplant recipients: FK506/MMF Dose-Ranging Kidney Transplant Study Group. *Transplantation* 69: 875, 2000.
35. Woodle, E. S. A randomized double blinded, placebo controlled trial of early corticosteroid cessation versus chronic corticosteroids maintenance therapy (Abstract 1511). *Am. J. Transplant.* 5: 540, 2005.
36. Gonwa, T., Mendez, R., Yang, H. C., et al. Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: Results at 6 months. *Transplantation* 75: 1213, 2003.
37. Mendez, R., Gonwa, T., Yang, H. C., et al. A prospective, randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: Results at 1 year. *Transplantation* 80: 303, 2005.
38. Ciancio, G., Burke, G. W., Suzart, K., et al. Daclizumab induction, tacrolimus, mycophenolate mofetil and steroids as an immunosuppression regimen for primary kidney transplant recipients. *Transplantation* 73: 1100, 2002.
39. Ciancio, G., Burke, G. W., Gaynor, J. J., et al. A randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate mofetil versus cyclosporine (NEORAL)/sirolimus in renal transplantation: II. Survival, function, and protocol compliance at 1 year. *Transplantation* 77: 252, 2004.
40. Vanrenterghem, Y., van Hooff, J. P., Squifflet, J. P., et al. Minimization of immunosuppressive therapy after renal transplantation: Results of a randomized controlled trial. *Am. J. Transplant.* 5: 87, 2005.
41. Rostaing, L., Cantarovich, D., Mourad, G., et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation* 79: 807, 2005.
42. Ciancio, G., Burke, G. W., Gaynor, J. J., et al. A randomized trial of three renal transplant induction antibodies: Early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation* 80: 457, 2005.
43. Ciancio, G., Burke, G. W., Suzart, K., et al. Efficacy and safety of daclizumab induction for primary kidney transplant recipients in combination with tacrolimus, mycophenolate mofetil, and steroids as maintenance immunosuppression. *Transplant. Proc.* 35: 873, 2003.
44. 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.
45. Kanitakis, J., Jullien, D., Petruzzo, P., et al. Clinicopathologic features of graft rejection of the first human hand allograft. *Transplantation* 76: 688, 2003.
46. Kanitakis, J., Petruzzo, P., Jullien, D., et al. Pathological score for the evaluation of allograft rejection in human hand (composite tissue) allotransplantation. *Eur. J. Dermatol.* 15: 235, 2005.
47. Lanzetta, M., Ayrout, C., Gal, A., et al. Experimental limb transplantation, part II: excellent return of function and indefinite survival after withdrawal of immunosuppression. *Transplant. Proc.* 36: 675, 2004.
48. Lee, W. P., Yaremchuk, M. J., Pan, Y. C., et al. Relative antigenicity of components of a vascularized limb allograft. *Plast. Reconstr. Surg.* 87: 401, 1991.
49. Kanitakis, J., Jullien, D., Nicolas, J. F., et al. Sequential histological and immunohistochemical study of the skin of the first human hand allograft. *Transplantation* 69: 1380, 2000.
50. Rush, D., Nickerson, P., Gough, J., et al. Beneficial effects of treatment of early subclinical rejection: A randomized study. *J. Am. Soc. Nephrol.* 9: 2129, 1998.
51. Rush, D. N., Jeffery, J. R., and Gough, J. Sequential protocol biopsies in renal transplant patients: Clinico-pathological correlations using the Banff schema. *Transplantation* 59: 511, 1995.
52. Shishido, S., Asanuma, H., Nakai, H., et al. The impact of repeated subclinical acute rejection on the progression of chronic allograft nephropathy. *J. Am. Soc. Nephrol.* 14: 1046, 2003.
53. Waaga, A. M., Gasser, M., Laskowski, I., et al. Mechanisms of chronic rejection. *Curr. Opin. Immunol.* 12: 517, 2000.
54. Jones, T. R., Humphrey, P. A., and Brennan, D. C. Transplantation of vascularized allogeneic skeletal muscle for scalp reconstruction in a renal transplant patient. *Transplantation* 65: 1605, 1998.
55. Wendt, J. R., Ulich, T., and Rao, P. N. Long-term survival of human skin allografts in patients with immunosuppression. *Plast. Reconstr. Surg.* 113: 1347, 2004.
56. Kanitakis, J., Jullien, D., Petruzzo, P., et al. Immunohistologic studies of the skin of human hand allografts: Our experience with two patients. *Transplant. Proc.* 33: 1722, 2001.
57. Rubin, R. H.. Infection in the organ transplant recipient. In R. H. Rubin and L. S. Young (Eds.), *Clinical Approach to Infection in the Compromised Host*, 4th Ed. New York: Kluwer Academic/Plenum Publishers, 2002.
58. Paya, C., Humar, A., Dominguez, E., et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cyto-

megalovirus disease in solid organ transplant recipients. *Am. J. Transplant.* 4: 611, 2004.
59. Fishman, J. A., and Rubin, R. H. Infection in organ-transplant recipients. *N. Engl. J. Med.* 338: 1741, 1998.
60. Reinke, P., Prosch, S., Kern, F., et al. Mechanisms of human cytomegalovirus (HCMV) (re)activation and its impact on organ transplant patients. *Transpl. Infect. Dis.* 1: 157, 1999.
61. Schneeberger, S., Lucchina, S., Lanzetta, M., et al. Cytomegalovirus-related complications in human hand transplantation. *Transplantation* 80: 441, 2005.
62. Nalesnik, M. A. Clinicopathologic features of posttransplant lymphoproliferative disorders. *Ann. Transplant.* 2: 33, 1997.
63. Penn, I. Post-transplant malignancy: The role of immunosuppression. *Drug Saf.* 23: 101, 2000.
64. Didlake, R. H., Dreyfus, K., Kerman, R. H., et al. Patient noncompliance: A major cause of late graft failure in cyclosporine-treated renal transplants. *Transplant. Proc.* 20: 63, 1988.
65. Preiksaitis, J. K., and Keay, S. Diagnosis and management of posttransplant lymphoproliferative disorder in solid-organ transplant recipients. *Clin. Infect. Dis.* 33 (Suppl. 1): S38, 2001.
66. Shroff, R., and Rees, L. The post-transplant lymphoproliferative disorder: A literature review. *Pediatr. Nephrol.* 19: 369, 2004.
67. Paya, C. V., Fung, J. J., Nalesnik, M. A., et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders: ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. *Transplantation* 68: 1517, 1999.
68. Kotton, C. N., and Fishman, J. A. Viral infection in the renal transplant recipient. *J. Am. Soc. Nephrol.* 16: 1758, 2005.
69. Opelz, G., and Henderson, R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 342: 1514, 1993.
70. A randomized comparative trial of Prograf (tacrolimus, FK506) in combination with azathioprine or mycophenolate mofetil (MMF) vs. Neoral (cyclosporine) with mycophenolate mofetil after cadaveric kidney transplantation: Three Year Report; Study Report on File; Data obtained with permission of Astellas Pharma US, Inc., 2000.
71. Andreoni, M., Goletti, D., Pezzotti, P., et al. Prevalence, incidence and correlates of HHV-8/KSHV infection and Kaposi's sarcoma in renal and liver transplant recipients. *J. Infect.* 43: 195, 2001.
72. Woodle, E. S., Hanaway, M., Buell, J., et al. Kaposi sarcoma: An analysis of the US and international experiences from the Israel Penn International Transplant Tumor Registry. *Transplant. Proc.* 33: 3660, 2001.
73. Kasiske, B. L., Snyder, J. J., Gilbertson, D. T., et al. Cancer after kidney transplantation in the United States. *Am. J. Transplant.* 4: 905, 2004.
74. Ramsay, H. M., Fryer, A. A., Hawley, C. M., et al. Non-melanoma skin cancer risk in the Queensland renal transplant population. *Br. J. Dermatol.* 147: 950, 2002.
75. Moloney, F. J., Kelly, P. O., Kay, E. W., et al. Maintenance versus reduction of immunosuppression in renal transplant recipients with aggressive squamous cell carcinoma. *Dermatol. Surg.* 30: 674, 2004.
76. Kasiske, B. L., Chakkera, H. A., and Roel, J. Explained and unexplained ischemic heart disease risk after renal transplantation. *J. Am. Soc. Nephrol.* 11: 1735, 2000.
77. Radermacher, J., Meiners, M., Bramlage, C., et al. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. *Transpl. Int.* 11: 3, 1998.
78. Pagano, G., Bruno, A., Cavallo-Perin, P., et al. Glucose intolerance after short-term administration of corticosteroids in healthy subjects: Prednisone, deflazacort, and betamethasone. *Arch. Intern. Med.* 149: 1098, 1989.
79. Diamant, S., and Shafrir, E. Modulation of the activity of insulin-dependent enzymes of lipogenesis by glucocorticoids. *Eur. J. Biochem.* 53: 541, 1975.
80. Ligtenberg, G., Hene, R. J., Blankestijn, P. J., et al. Cardiovascular risk factors in renal transplant patients: Cyclosporin A versus tacrolimus. *J. Am. Soc. Nephrol.* 12: 368, 2001.
81. Klein, I. H., Abrahams, A., van Ede, T., et al. Different effects of tacrolimus and cyclosporine on renal hemodynamics and blood pressure in healthy subjects. *Transplantation* 73: 732, 2002.
82. Morales, J. M., Andres, A., Rengel, M., et al. Influence of cyclosporin, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation. *Nephrol. Dial. Transplant.* 16 (Suppl. 1): 121, 2001.
83. Kasiske, B. L., Snyder, J. J., Gilbertson, D., et al. Diabetes mellitus after kidney transplantation in the United States. *Am. J. Transplant.* 3: 178, 2003.
84. Duijnhoven, E. M., Boots, J. M., Christiaans, M. H., et al. Influence of tacrolimus on glucose metabolism before and after renal transplantation: A prospective study. *J. Am. Soc. Nephrol.* 12: 583, 2001.
85. Francois, C. G., Breidenbach, W. C., Maldonado, C., et al. Hand transplantation: Comparisons and observations of the first four clinical cases. *Microsurgery* 20: 360, 2000.
86. Yocum, D. E., Furst, D. E., Bensen, W. G., et al. Safety of tacrolimus in patients with rheumatoid arthritis: Long-term experience. *Rheumatology (Oxford)* 43: 992, 2004.
87. Squifflet, J. P., Backman, L., Claesson, K., et al. Dose optimization of mycophenolate mofetil when administered with a low dose of tacrolimus in cadaveric renal transplant recipients. *Transplantation* 72: 63, 2001.
88. Casez, J. P., Lippuner, K., Horber, F. F., et al. Changes in bone mineral density over 18 months following kidney transplantation: The respective roles of prednisone and parathyroid hormone. *Nephrol. Dial. Transplant.* 17: 1318, 2002.
89. Canalis, E. Mechanisms of glucocorticoid-induced osteoporosis. *Curr. Opin. Rheumatol.* 15: 454, 2003.
90. van den Ham, E. C., Kooman, J. P., Christiaans, M. L., et al. The influence of early steroid withdrawal on body composition and bone mineral density in renal transplantation patients. *Transpl. Int.* 16: 82, 2003.
91. Epstein, S. Post-transplantation bone disease: The role of immunosuppressive agents and the skeleton. *J. Bone Miner. Res.* 11: 1, 1996.
92. Frazier, P. A., Davis-Ali, S. H., and Dahl, K. E. Correlates of noncompliance among renal transplant recipients. *Clin. Transplant.* 8: 550, 1994.
93. Sketris, I., Waite, N., Grobler, K., et al. Factors affecting compliance with cyclosporine in adult renal transplant patients. *Transplant. Proc.* 26: 2538, 1994.
94. Kiley, D. J., Lam, C. S., and Pollak, R. A study of treatment compliance following kidney transplantation. *Transplantation* 55: 51, 1993.
95. Thorp, M., DeMattos, A., Bennett, W., et al. The effect of conversion from cyclosporine to tacrolimus on gingival hyperplasia, hirsutism and cholesterol. *Transplantation* 69: 1218, 2000.
96. Face transplant patient uses new lips to smoke: Doctors fear habit will interfere with healing, raise risk of tissue rejection. Available at: http://www.msnbc.msn.com/id/10912182. Accessed cited January 18, 2006.
97. Furr, A., Wiggins, O., Vasilic, D., et al. A discussion of the psychosocial implications of disfigurement and the future of human face transplantation. *Plast. Reconstr. Surg.* (in press).