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Review article

Renal transplantation, immunosuppression and the skin: an update

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Transplant medicine has seen many innovations over past decades and continues to evolve into the 21st century. Newer immunosuppressive strategies in renal transplantation are associated with better patient and graft survival rates; however, the adverse toxicities and long-term side effects associated with these agents present a number of challenges. Certain immunosuppressants are commonly used in dermatologic disorders, however, dermatologists may be less familiar with the clinical efficacy, side-effect profile, and dosage of newer immunosuppressive agents. A knowledge of the molecular and cellular mechanisms of action of these agents gives us a better understanding of how these agents contribute to the cutaneous and mucosal complications frequently seen post-transplant. With the advent of new immunosuppressive therapies and different treatment regimens, there is an increasing need for a multidisciplinary approach to balancing the risks and benefits of these medications to the individual transplant recipient. This review will highlight the different immunosuppressive agents and their effect on the skin while focusing on the evidence base to support the commonly used immunosuppressive regimes, newer protocols aimed at achieving maximum graft survival with minimal side effects, and important drug interactions with which all dermatologists should be familiar.

Key words: **drug interactions; immunosuppression; renal transplantation; skin cancer.**

Skin cancers occur more frequently in renal transplant recipients (RTRs) relative to the general population especially squamous cell and basal cell carcinomas (SCC and BCC) of the skin, but also the less common cutaneous malignancies (Table 1). Over 90% of their skin cancers occur on habitually sun-exposed sites indicating the association between skin cancer post-transplant and cumulative ultraviolet light exposure post-transplant. There is a marked preponderance of SCC with a ratio of 3 : 1 (SCC : BCC), a reversal of the usual ratio in the non-transplanted population. Older age, male gender, and longer durations on immunosuppression are all associated with increased risk of non-melanoma skin cancer post-transplant (1). Factors such as blue or hazel eyes and childhood sun exposure also contribute to increased risk (2). There is good emerging evidence of the role of oncogenic viruses acting as co-factors with ultraviolet radiation (UVR) in the pathogenesis of skin cancers post-transplantation. The combination of systemically immunosuppressing drugs and the local immunosuppressive effect of UVR, promote human papilloma virus replication, which in turn leads to oncogenic effects in the skin (3).

The changing face of immunosuppression

Prior to 1960, strategies to reduce rejection of a transplanted kidney included whole-body irradiation, splenectomy, thymectomy, and thoracic duct drainage. The introduction of azathioprine to reduce rejection rates followed thereafter by the addition of corticosteroids heralded the beginnings of modern immunosuppression. Initial 1-year graft survival was approximately 50% (4). Polyclonal antibody preparations, anti-thymocyte globulin, and anti-lymphocyte globulin began routine use in the 1970s, but their side-effect profile and inability to standardize the product limited their use.

The next significant development in renal transplantation occurred in the 1980s with the introduction of the calcineurin inhibitor (CI), ciclopsporin. Four-year graft survival increased to 70% when ciclosporin was used alone compared with 62% for conventionally treated groups (5). It became apparent, however, that ciclosporin caused significant acute and chronic nephrotoxicity and the search continued for less nephrotoxic agents (6). The licensing of muromonab (OKT3) in 1987 by the FDA was a significant milestone in the prevention and treatment of acute

Table 1. Cutaneous tumours with increased incidence post transplant

1. Squamous cell carcinoma
2. Basal cell carcinoma
3. Malignant melanoma
4. Kaposi's sarcoma
5. Merkel cell tumour
6. Cutaneous B-cell lymphoma
7. Cutaneous T-cell lymphoma
8. Natural killer-cell lymphoma
9. Angiosarcoma
10. Malignant fibrous histiocytoma
11. Leiomyosarcoma
12. Dermatofibrosarcoma protuberans
13. Sebaceous carcinoma

rejection, with activity against a single antigen, the T-cell receptor CD3 complex. Since then, two monoclonal antibodies, basiliximab and dacluzimab, both of which are IL-2 receptor blocking antibodies, have become licensed for induction therapy.

Ten years later, randomized trials comparing tacrolimus with ciclosporin showed that tacrolimus is a more effective primary agent than cyclosporine in preventing acute rejection (7). Likewise, mycophenolate mofetil (MMF), a new anti-metabolite, was found to be a more efficacious agent when compared with azathioprine in triple immunosuppression regimes, with less acute rejection (8). Sirolimus became available in 1999, and is used to reduce the required dose of ciclopsporin in certain immunosuppressive regimes. The role of newer agents, like everolimus, in immunosuppressive protocols remains to be determined.

Principles of immunosuppression

Combination therapy uses drugs with different modes of action to enhance immunosuppression, allowing lower doses to be used and reducing the dose-related side effects. Most immunosuppressive regimes combine a CI with an adjunctive agent and steroids (Table 2). Adjunctive agents are used in combination with CIs to enhance the potency of the immunosuppressive protocol as measured by a decreased incidence of acute rejection. Previously, 1-year patient and graft survival were standard end points to compare the efficacy of agents/regimes. However, as most regimes now exceed 90% patient and graft survival at 1 year, the incidence of acute rejection is now also used as an end point when assessing new agents. In the last two decades, the incidence of acute rejection has fallen towards 10–15%. It is now increasingly difficult to prove the significance of small improvements in acute rejection and emphasis is shifting towards prevention of late graft loss. The use of more potent immunosuppressive agents to lower frequency of acute rejection and thus lower the incidence of late graft loss must be balanced against the increased potential for toxicity, infection, skin cancers and other malignancies. Work continues to develop a gold standard agent aimed at achieving tolerance (host immunological unresponsiveness to the transplant with an otherwise fully functioning immune system).

Calcineurin Inhibitors

Ciclosporin is a polypeptide of fungal origin initially introduced as an oral solution (Sandimmun®, Novartis Pharma AG, Basel, Switzerland) and subsequently in microemulsion formulation (Neoral®, Novartis Pharma AG, Basel, Switzerland), which improved the bioavailability (9). Monitoring for nephrotoxicity and elevated blood pressure is particularly important on ciclosporin. Tacrolimus (Prograf®, Fujisawa, Killorglin, Co. Kerry, Ireland) was initially called FK506 and is increasingly being used in new kidney transplant recipients. Diabetic potential is significant, with hyperglycaemia or frank diabetes occurring in nearly 20% of patients receiving tacrolimus-based immunosuppression (10). In practice, the choice of CI will be modified based on individual patient risk profiles. Mayer at al. (11) compared tacrolimus- and ciclosporin-based immunosuppressive regimens and showed no difference in patient or graft survival at 1 year but tacrolimus was associated with a lower incidence of biopsy-confirmed acute rejection. Five-year follow-up data suggest that tacrolimus-based therapy significantly reduces risk of graft failure and side effects, with less patients requiring treatment for hypertension and hyperlipidaemia compared with ciclosporin-based therapy (10). Other studies in living donor kidney transplantation, however, suggest that ciclosporin-based therapy is superior to tacrolimus-based therapy in prolonging graft survival (12). Cosmetically, unlike with ciclosporin, hypertrichosis, gum hypertrophy, and sebaceous gland hyperplasia do not develop with long-term tacrolimus use. Such cosmetic issues are of particular concern in female and younger patients. It is worth remembering that the commonest cause of graft failure in young people is non-compliance with immunosuppressants. Serum levels of both drugs require close monitoring because of their nephrotoxic potential. While tacrolimus trough levels correlate well with drug exposure, research now suggests that levels 2 h after a dose (C2 monitoring) may be more reflective of drug exposure, particularly with the microemulsion formulation (Neoral®) (13). In practice, 2 h monitoring may prove logistically difficult to perform.

Table 2. Post-transplantation immunosuppressants and their main cutaneous side effects

Drug categories	Drug	Comments	Reported cutaneous adverse effects*
Calcineurin inhibitors	Ciclosporin	Introduced in 1983 Inhibits T-cell function by impairing IL-2 and cytokine release Increases TGF-B expression Induction and maintenance therapy Metabolized by cytochrome P-450 in the liver Drug level monitoring important Main S/E: nephrotoxicity, hyperlipidaemia, neurotoxicity, gout	Gingival hyperplasia (C) Hypertrichosis (C) Sebaceous hyperplasia (C) Acne (C) Flushing (C) Burning of hands and feet (during first week) (C) Alopecia (C) Pruritis (C)
	Tacrolimus (FK506)	Macrolide antibiotic introduced in 1994 Shares many properties and mechanism of action with ciclosporin Used as both initiation and rescue therapy Metabolized by cytochrome P-450 Monitor whole-blood trough levels Main S/E: nephrotoxicity, diabetogenic, neurotoxicity, hypertension, gastrointestinal upset	Pruritus (C) Alopecia (C) Diaphoresis (C) Ecchymoses (C) Photosensitivity (R) Hirsutism (R) Lyell's Syndrome (R) Stevens-Johnson's (R)
Adjunctive Agents	Azathioprine	First 'true' immunosuppressant employed in renal transplants (1961) An anti-proliferative derivative of 6-mercaptopurine Inhibits RNA synthesis, and hence reduces T-cell production Role as maintenance therapy Heterozygotes and homozygotes for a polymorphism in the gene for thiopurine methyl transferase have increased risk of myelosuppression Main S/E: hepatitis, alopecia, pancreatitis, reduce dose with allopurinol	Exanthems (R) Hypersensitivity (R) Aphthous stomatitis (R) Alopecia (R)
	Mycophenylate mofetil	More selective T/B-cell inhibitor introduced in 1994 Reversible inhibitor of inosine monophosphate dehydrogenase Essentially blocks the proliferation of lymphocytes Maintenance and may have a role in preventing chronic rejection Main S/E: gastrointestinal upset, diarrhoea, bone marrow suppression	Moniliasis (C) Peripheral oedema (C) Acne (C) Alopecia (R)
	Sirolimus	Macrolide antibiotic introduced in 1999 Not a calcineurin inhibitor, but does bind to FKBP (mTOR inhibitor) Maintenance and chronic rejection Mutiple SE's although not nephrotoxic Pulmonary toxicity, hypertension, dyslipidaemia, arthralgia, insomnia, hypokalaemia, thrombocytopenia	Acne (C) Delayed wound healing (C). Eyelid oedema (C) Mouth ulcers (C) Lymphoedema (R) Angioedema (R)
	Corticosteroids	Non-specific anti-inflammatory agents Inhibit cytokine-producing genes in T cells Induction, maintenance, and acute rejection Main S/E: hypertension, cosmetic changes, osteoperosis, hyperlipidemia, diabetes, and cataracts	Acne (C) Dermal thinning (C) Purpura (C) Telangiectasia (C) Striae (R)

*Immunosuppressive regimens involving combinations of drugs are associated with increased rates of malignancy and opportunistic infections of the skin. Non-specified 'rash' has been reported with all the above agents. This table contains the commoner reported cutaneous side effects. S/E, side effects; C, common side effects; R, rarer side effects.

Anti-metabolites

MMF (Cellcept®, Hoffman-la-Roche, Basel, Switzerland) has largely replaced azathioprine in triple drug regimens in most centres for newly transplanted patients. Patients stable on older combinations of drugs, however, are rarely changed to newer formulations. Three large randomized double-blind trials comparing MMF with azathioprine, in patients on ciclosporin and steroids, showed no significant effect on survival at 3 years.

Despite this, MMF was shown to reduce the incidence of acute rejection by almost 50% at 6 months (14). In addition, MMF significantly reduced the incidence of chronic allograft failure independently of the presence or absence of acute rejection (15). Unlike azathioprine, MMF does not interact with allopurinol, used for prophylaxis of gout, commonly seen after transplantation.

Mammalian target of rapamycin (mTOR) inhibitors

Sirolimus (Rapamune®, Wyeth, Hampshire, UK), previously known as rapamycin, gained FDA approval in 1999. It represents another class of immunosuppressant drug with a similar structure to tacrolimus

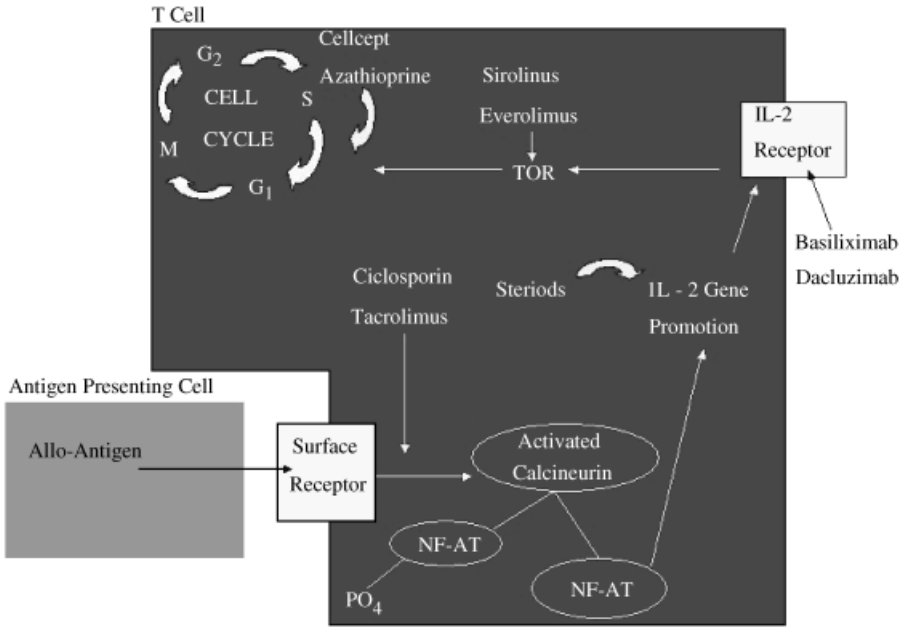

Fig. 1. Schematic representation of the sites of action of presently available immunosuppressive agents. NF-AT, nuclear factor of activated T cells; TOR, target of rapamycin.

although it does not inhibit calcineurin. It inhibits a multifunctional serine–threonine kinase, mTOR that is involved in an alternative pathway of T-cell activation (Fig. 1).

Sirolimus is indicated as an adjunctive agent, in combination with ciclosporin and steroids. In clinical trials, a combination of sirolimus, corticosteroids and reduced dose ciclosporin was associated with a lower incidence of acute rejection compared with patients receiving azathioprine, standard doses of ciclosporin, and corticosteroids (16). Similar low rejection rates were seen on combining sirolimus with tacrolimus (17). Sirolimus is less nephrotoxic than ciclosporin or tacrolimus; however, hypercholesterolemia and hypertriglyceridemia occur in about 50% of sirolimus-treated patients. Delayed wound healing and pulmonary toxicity are other potentially serious complications (18). Everolimus, a newer mTOR inhibitor, similarly, has been shown to enhance the immunosuppressive action of ciclosporin-based regimens.

Rejection of the transplanted kidney

Rejection can be divided into the following categories; hyperacute (occurring within minutes to hours of release of clamps), accelerated acute (within 24 h to 4 days post-transplant), acute (usually occurs days to weeks after transplant), and chronic (occurring over months to years).

Hyperacute rejection is irreversible and results from preformed circulating antibodies, and is very rare if pre-transplant cross-matching between donor and recipient is performed.

Accelerated acute rejection is a result of prior sensitization of the recipient to donor antigens (transfusions or prior transplants) and mediated by both cellular and humoral immunity.

Approximately, 90% of cases of acute rejection are cellular mediated and easier to treat than the 5–10% that are humoral mediated. Patients with acute rejection develop constitutional symptoms because of cytokine release.

The aetiology of the progressive loss of renal function seen in chronic rejection is not fully understood, but probably represents a combination of immune and non-immune mechanisms, drug toxicity, chronic ischemia, and repeated bouts of acute rejection.

Induction therapy

Induction therapy is a strategy to avoid early acute rejection. Antibody-based therapy (Table 3) is used in the early post-transplant period for up to 8 weeks. A combination of CI, MMF and IL-2 receptor antagonists (basiliximab or daclizumab) lowers the incidence of early acute rejection by approximately 15% compared with placebo (19, 20). However, these newer monoclonals are not indicated for treatment of established rejection. Their use must be weighed against their cost and their potential to cause malignancy in the long term. Evidence suggests that they are of most benefit in high immunologic risk patients.

Table 3. Other post-transplant medications

Antibody induction	OKT3 (monoclonal antibody) ATG (anti-thymocyte globulin – polyclonal antibody)	Antibodies bind to the CD3 receptor (found on all T lymphocytes) and lead to opsonization Used as 'induction' agents, and occasionally in acute rejection High incidence of serious infection and Epstein–Barr virus-related lymphomas
	Anti-CD3 (monoclonal antibody)	Murine monoclonal antibody Blocks T-cell function Used for induction and acute rejection S/E: cytokine release syndrome and pulmonary oedema
	Basiliximab (chimeric) Daclizumab (humanized)	Newer induction agents, not used for rejection Bind to IL-2 receptor on T cells, expressed only on activated lymphocytes Better tolerated, and allow lower doses of CI to be used initially Few S/E but long-term S/E unknown
Supplementary agents	Calcium channel blockers Statins	Anti-hypertensive and allow reduction of ciclosporin dose As part of a lipid-lowering regime
Infection prophylaxis	Triphetoprim – sulphamethoxazole Anti-virals	Anti-microbial prophylaxis against pneumocystosis, listeriosis CMV prophylaxis recommended for high-risk patients

S/E, side effects.

Drug minimization/reduction regimens

In an attempt to reduce toxicity and long-term complications, certain centres use multiple immunosuppressive agents early after renal transplantation to reduce the risk of acute rejection and then withdraw one or more agents. This practice reflects the new era of immunosuppressive agents and was not considered an option with many of the older regimens. Cessation of immunosuppressive medications for patients, in whom skin cancer developed after transplantation, results in deceleration of cutaneous carcinogenesis, decreased verrucae, and improved skin quality within 1–2 years (21). Reduction of immunosuppression has also been shown to reduce the risk of metastatic spread in transplant recipients with aggressive SCC (22).

Calicineurin inhibitors reduction/cessation

A number of randomized multicentre trials have compared protocols that withdraw, minimize, or avoid CIs (23–25). The withdrawal of ciclosporin is beneficial in that it improves renal haemodynamics, blood pressure, and lipids. While the long-term graft survival rates were similar in patients withdrawn from ciclosporin compared with the standard regime, the incidence of acute rejection in the withdrawal group was higher. The addition of sirolimus (26), MMF, IL-2 receptor antagonists, and combinations thereof has shown acceptable graft survival rates and acute rejection rates, although further research is warranted.

Steroid withdrawal/avoidance

As yet there is no consensus regarding the non-use or withdrawal of steroids post-transplantation.

Kasiske et al. (27) confirmed increased prevalence of late episodes of AR and chronic allograft nephropathy after initial successful discontinuation of steroids. The same meta-analysis indicated a higher incidence of acute rejection after ciclosporin withdrawal but no long-term effects on graft survival. Studies on regimens incorporating ciclosporin, MMF, and steroids, with no acute rejection at 90 days, have reported small increases in the incidence of acute rejection when steroids are tapered (28). The addition of basiliximab induction to this maintenance regimen showed no increased risk of acute rejection with rapid and early corticosteroid withdrawal. A pilot study of rapid discontinuation of steroids at day 6 post-transplantation in living donor kidney transplant recipients showed no increased risk of acute rejection or graft loss (29). Regimens incorporating tacrolimus, MMF or sirolimus and steroids may be safer but have not been compared in head-to-head trials. Smaller steroid sparing trials with anti-IL-2 induction suggest that the addition of basiliximab may lessen subsequent risk of acute rejection (30). Prospective, randomized, controlled, double-blinded studies to examine withdrawal of corticosteroids during the first week post-transplant are ongoing.

Immunosuppressive treatment and skin cancer risk

The comparison of studies to identify the relative contribution of individual immunosuppressants to skin cancer risk post-transplantation is limited by different study methodologies, the use of combination

therapies, and the introduction of different agents in different eras. Some report ciclosporin conferring an increased risk of skin cancer relative to other immunosuppressive agents (31–37) while others point to azathioprine as conferring a greater risk (38–41). Other studies conclude that there is no significant difference in skin cancer risk between the agents (42–46). Previously, increased cancer risk post-transplantation was believed to represent a failure of the immune system to eliminate cancerous cells; however, recent work suggests that ciclopsporin might alter cells and promote tumour progression directly by inducing the synthesis of TGF-β. (47) A further study showed tacrolimus to have a similar effect on tumour progression and TGF-β1 expression (48). The results of studies comparing tacrolimus and ciclosporin are contradictory (49, 50). The potential advantage of reduced cancer risk for sirolimus and sirolimus derivatives has been proposed (51). Initial data, at 2 years post-transplantation, suggest that malignancy rates are lower for patients receiving sirolimus-based therapy without ciclosporin or for patients on sirolimus maintenance therapy after early ciclosporin withdrawal (52).

Drug interaction between immunosuppressants and drugs used in dermatology

Transplant recipients are in general quite knowledgeable in relation to the dangers of other drugs interacting with their immunosuppression. It is good practice to be aware of the mechanism of action of immunosuppressant agents and to check the drug formulary if unsure of interactions. The most commonly used agents (cyclosporin, tacrolimus and sirolimus) all have a narrow therapeutic index and show considerable inter-individual variation in their pharmacokinetics. This pharmacokinetic variability is in part because of the human cytochrome p450 system enzyme CYP3A4 and also the efflux pump P-glycoprotein (ABCB1/MDR1) (53, 54). P-glycoprotein is located within the brush border of enterocytes where it acts to pump a wide variety of xenobiotics out of the cell cytoplasm and into the intestinal lumen. There is a striking overlap between the list of drugs that act as substrates for CYP3A4 and inhibitors of P-glycoprotein. Co-administration of such drugs act to decrease the metabolism and increase the bioavailability of cyclosporin, tacrolimus and sirolimus. Table 4 outlines potential interactions between immunosuppressant agents and drugs commonly used in dermatology.

Table 4. Dermatology drugs that interact with immunosuppressant drugs

Drug group	Interacting effect
CYP3A4 inhibitors	
Erythromycin	Inhibition of CYP3A4
Clarithromycin	⇒ Decreased metabolism of drug
Itraconazole	⇒ Increased blood levels of ciclosporin,
Ketoconazole	tacrolimus, and sirolimus
Miconazole	⇒ Increased risk of toxicity (nephrotoxicity,
Fluconazole*	neurotoxicity, myelosuppression) and
Clotrimazole*	excessive immunosuppression (infections
Dapsone*	and post-transplant lymphoproliferative disorders)
CYP3A4 inducers	
Rifampicin	Increased expression of CYP450
Glucocorticoids	⇒ Increased 3A4 enzyme activity
	⇒ Increased drug metabolism
	⇒ Decreased blood level of ciclosporin, tacrolimus, and sirolimus
	⇒ Increased risk of acute allograft rejection
Anti-virals	
Acyclovir (oral)	Increased risk of nephrotoxicity/neurotoxicity with ciclosporin or tacrolimus
Ganciclovir	Increased risk of myelosuppression with azathioprine, MMF, or sirolimus

*Minor interaction.

Summary

Transplant recipients develop a unique set of dermatologic problems, many of which can be attributed to their immunosuppressive therapies. Emerging trends in immunosuppression include regimens that withdraw or reduce the total immunosuppressive load to which patients are exposed over time. In addition, newer agents, the mTOR inhibitors, may be less carcinogenic than their predecessors. Close collaboration between dermatologists and all other healthcare professionals involved in the care of transplant recipients is vital. Patient education, skin screening programmes, chemoprophylaxis, and protocols for the prompt management of skin cancers remain the key to providing best dermatologic care post-transplantation.

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