Immunosuppressants and Skin Cancer in Transplant Patients: Focus on Rapamycin

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BACKGROUND. **The responsibility of immunosuppressants for the increased risk of skin cancers in organ transplant recipients is widely recognized. Discerning the role of each drug is complicated owing to the fact that most patients generally have combinations of several medications.**

OBJECTIVE. **This article will discuss the role of the main immunosuppressants in the pathogenesis of skin cancers.**

METHODS. **This work consists of a review of the most significant publications.**

RESULTS. **Experimental and clinical studies suggest that corticosteroids, azathioprine, cyclosporine (CsA), and tacrolimus increase the incidence of skin cancer. Each drug may act through two different mechanisms including the impairment of the systemic immunosurveillance and a direct oncogenic effect. CsA was shown to be oncogenic independently of its immunosuppressive effect. By contrast, several works on mice have found that rapamycin inhibits tumor growth while being immunosuppressive. Furthermore, rapamycin was shown to inhibit several UV-induced mechanisms involved in skin carcinogenesis. Preliminary clinical studies have reported a lower incidence of skin malignancy in patients treated with rapamycin compared to CsA from the time of transplantation.**

CONCLUSION. **New immunosuppressive strategies for transplant patients with skin cancer are not only based on minimizing immunosuppression. Data suggest that rapamycin could have a protective effect against skin cancer. Further studies are required to assess accurately the efficacy and tolerance of rapamycin in these patients.**

SYLVIE EUVRARD, MD, CLAAS ULRICH, MD, AND NICOLE LEFRANCOIS, MD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

THE RESPONSIBILITY of immunosuppressive treatments for the increased risk of skin cancers in organ transplant recipients is widely recognized,[1,2] and the decrease of tumors after reduction or cessation of treatments has been documented.[3–5] Nevertheless, the relative contribution of each immunosuppressive drug to the development of skin cancer remains difficult to assess for several reasons. First, skin cancers appear at an average of 8 to 9 years after graft for patients grafted at around 40 years and far later for younger patients. The second reason is the fact that "dermatologic factors" intervene. They are mainly ultraviolet radiation, skin type, and susceptibility to sunburn. Furthermore, several genetic factors have shown to be associated with the occurrence of skin cancers and include polymorphisms in p53 codon 72,[6–8] glutathione *S*-transferases,[9,10] and interleukin-10 promoter.[11] It is often difficult to know in which proportions all these factors intervene. For some patients, the role of heavy sun exposure is crucial and the role of the immunosuppressive treatment is probably less important. By contrast, other patients whose sun exposure past history is moderate seem to be more sensitive to variations in dosages or qualities of immunosuppressive drugs. This article will discuss the role of each immunosuppressive drug in the pathogenesis of skin cancers and will present the current data on rapamycin as an agent that may be less oncogenic and potentially protective against skin cancer in transplant patients.

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Immunosuppressants and Skin Cancers: Review of Medications

There are two different mechanisms by which medications may contribute to skin cancer development. They include the impairment of the systemic immunosurveillance and a direct oncogenic effect. Discerning the relative contributions of each immunosuppressive drug is complicated by the fact that immunosuppression regimens involve combinations of two, three, and occasionally four medications.[12] We will review the clinical data regarding the pathogenic role of the common medications as it relates to the development of skin cancer. Data that demonstrate a direct carcinogenic role of medications is limited to cyclosporine (CsA), but this mechanism may be relevant to other medications as well.

ISSN: 1076-0512/04/$15.00/0 • Dermatol Surg 2004;30:628–633

OKT3

OKT3 was the first monoclonal antibody introduced in clinical practice in the early 1980s and was used primarily for prophylaxis of organ rejection. It is one of the most potent immunosuppressive agents and is still given for steroid-resistant transplant rejection generally over a 10-day course. One study reported that OKT3 use was associated with an increased risk in skin cancer in heart transplant patients.[13] Nevertheless, several other works performed on kidney,[14,15] heart,[16] and liver transplant patients[17] showed no significant association.

Corticosteroids

Since the inception of transplantation, corticosteroids have widely been used as prophylactic and curative treatments of rejection. Their role was studied among users of oral corticosteroids other than organ transplant patients[18] and it was found that the risk of skin cancer was increased especially for squamous cell carcinomas and modestly for basal cell carcinomas.

Azathioprine

Azathioprine is a purine analog which inhibits purine synthesis and metabolism. It is effective in preventing the onset of acute rejection and has been given to transplanted patients since the early 1960s.[12] Renal transplant recipients with skin cancers were found to have increased concentrations of the active azathioprine metabolite 6-thioguanine nucleotide in red blood cells compared to patients without skin cancer, although there was no significant difference between patients and control in azathioprine dosage.[19] This was explained later by the role of genetic variation in thiopurine methyltransferase activity.[20] The effects of azathioprine, prednisolone, cyclophosphamide, and CsA on UV-induced skin carcinogenesis were studied in the albino hairless (HRA/Skh-1) mouse. Following 30 weeks of exposure, 87% of mice developed skin tumors. All drugs were given at immunosuppressive levels. Azathioprine was found to have strong promoting effects and induced the largest proportion of carcinomas.[21]

Calcineurin Inhibitors

CsA and tacrolimus are similar in their action mechanism and clinical efficacy although their side effects profiles show some differences. They inhibit calcineurin which promotes cytokine gene activation. Inhibition of calcineurin prevents expression of several cytokine genes such as the IL-2 gene.

CsA

The introduction of CsA in the 1980s has provided a major impact on the outcome of organ transplantation. CsA is a small cyclic peptide produced by a fungus isolated from Norwegian soil. CsA inhibits interleukin-2 and enhances the expression of transforming growth factor-β (TGF-β), which also inhibits interleukin-2-stimulated T-cell proliferation and the generation of cytotoxic T lymphocytes. Murine UVR-induced tumors selected for their inability to grow in normal recipients were shown to be capable of progressive growth following their transplantation to syngeneic mice treated by CsA.[22] Patients treated by a combination of corticosteroids, azathioprine, and CsA were found to have a threefold increase in risk of skin cancer as compared to patients under bitherapy (corticosteroids and azathioprine).[23,24] Other large series reported also that lesions occurred earlier in patients treated by CsA.[16,24,25] Both these facts were thought to be related to a deeper immunosuppression because all the studies compared tritherapy with bitherapy. Furthermore, a 5-year randomized prospective study showed that low-dose CsA regimens were associated with a lower incidence of tumors than was standard therapy,[26] and it was widely admitted that the increased risk of skin cancer in transplant patients was independent of the agent used and was the result of the immunosuppression per se.[27] New data suggest that CsA can promote cancer progression by a direct cellular effect that is independent of its effect on the host's immune cells.[28] These experiments were carried out ex vivo to avoid any confounding effects of CsA on in vivo immune surveillance mechanisms. CsA treatment of adenocarcinoma cells transformed noninvasive cells (cuboidal epithelial aspect) to invasive cells (marked membrane ruffling and formation of numerous pseudopodia with increased cell motility). It was shown that these phenotypic changes were dose-dependent and reversible and could be prevented by treatment with monoclonal antibodies directed at TGF-β. In vivo, CsA was found to enhance tumor growth of several tumor cell lines in T-cell-, B-cell-, and natural killer-cell deficient severe combined immune deficiency (SCID)-beige mice. Anti-TGF-β monoclonal antibodies but not control antibodies prevented the CsA-induced increase in the number of metastases suggesting CsA-induced TGF-β production is involved in this mechanism.

Tacrolimus

Tacrolimus is a macrolide antibiotic isolated from a soil actinomycete. It blocks T-cell activation by a mechanism similar to that of CsA and was initially

approved by the Food and Drug Administration in 1994 for use in liver transplant recipients. Several large series have shown that skin cancers are the most common malignant conditions in liver transplant recipients.[17,29,30] Furthermore, in vitro studies on human hepatoma cells have found that tacrolimus promotes tumoral cell growth.[31] It is still difficult to know if the incidence of skin cancer is lower in patients treated with tacrolimus compared to patients with CsA, the results of studies being contradictory.[29,32] Although tacrolimus also increases TGF-β transcription rates in humans, this may be less prevalent than with CsA, suggesting that tacrolimus could be less oncogenic.[33]

Mycophenolate Mofetil

Mycophenolate mofetil is the ethyl ester of the fungal antibiotic mycophenolic acid, which inhibits the de novo purine biosynthesis pathway. It was approved for use in kidney transplant recipients in 1995 and is currently widely used in replacement of azathioprine. A recent communication reported a prospective observational cohort study using primary source data from large renal transplant registries based in North America (United network for Organ Sharing [UNOS] and Europe Collaborative Transplant Study [ECTS]). The study found that patients receiving mycophenolate mofetil were not at an increased risk of developing lymphoma compared to patients receiving other immunosuppressive treatments.[34] No information is available on skin malignancies.

FTY 720

FTY 720 is a synthetic analog of a compound derived from a fungus. It is a novel immunosuppressant to be developed for use in organ transplantation in combination with CsA. Its mechanism of action seems to be distinct from any other drug.[35] FTY reduces circulating lymphocytes via induction of the accelerated homing of lymphocytes to lymph nodes and Peyer's patches. Antitumoral properties were recently reported on human bladder and breast cancer lines in vitro and in vivo.[36,37] Furthermore, at low doses FTY 720 was shown to inhibit the morphologic changes as a result of CsA and to induce apoptosis of the CsA-treated cancer cells at high doses.[38] The authors did not find the marked increase of TGF-β1 in the medium of CsA-treated T24 cells as described in CsA-treated A-549 cells by Hojo et al.,[28] suggesting that the production of TGF-β stimulated by CsA is dependent on the variety of cancer cells.

Immunosuppressants and Skin Cancers: Review of Properties of Rapamycin

Background and Mechanism of Action

Rapamycin and its derivatives, CC1-779 and everolimus, are promising antitumor agents that act by inhibition of mTOR.[39–41] The mammalian target of rapamycin (mTOR), also designated FKBP12 and rapamycin-associated protein (FRAP), rapamycin and FKBP12 target 1 (RAFT1), rapamycin target 1 (RAPT1), or sirolimus effector protein (SEP), a serine/threonine kinase, was identified as the mammalian counterpart of yeast TOR and is considered a member of P13K family kinases.

Rapamycin (Rapamune, Wyeth, Madison, NJ) is a bacterial macrolide antibiotic produced by a strain of *Streptomyces hygroscopicus* isolated from a soil sample collected from Rapa Nui, commonly known as Easter Island. Initially isolated as an antifungal agent, rapamycin (also named sirolimus) was shown to reveal impressive antiproliferative and immunosuppressive properties. The molecular mechanism underlying these various properties is the same. As a structural analog of the macrolide antibiotic FK 506, rapamycin forms a complex with the intracellular protein FK-binding protein-12 (FKBP12), which binds with high affinity to the mTOR. The inhibition of mTOR causes dephosphorylation and inactivation of p70 ribosomal protein S6 kinase resulting in the blockage of cell-cycle progression at the juncture of G1 and S phase, consequently inhibiting IL-2 stimulation of lymphocyte division and antibody production. Clinical studies in kidney transplant patients have confirmed that rapamycin is a potent immunosuppressive agent used in base therapy or in association with CsA.

In Vitro Antineoplastic Properties

Several studies have shown that rapamycin inhibits the growth of many malignant cells in culture (rhabdomyosarcoma, neuroblastoma and gliobastoma, small cell lung cancer, osteosarcoma, pancreatic cancer, breast and prostate cancer, murine melanoma and leukemia, B-cell lymphoma).[40,41] The effect of rapamycin on renal cancer cell phenotype and molecules implicated in tumor progression was recently assessed.[42] Rapamycin conditioning transformed renal cancer cells selected for invasive phenotype (spindle- or dome-shaped cells with pseudopodia) in noninvasive cuboidal cells that formed cell-to-cell adhesions. These effects were inhibited by the addition of tacrolimus suggesting the essential role of the binding of FKBP12. Furthermore, rapamycin up-regulated E-cadherin expression, increased p27kipl, reduced

cyclinD1, and arrested the growth of renal cancer cells in G1/S phase.

mTOR Protein and Ultraviolet Radiation

Various UVB-induced cellular mechanisms involved in cutaneous carcinogenesis seem to be mediated by the mTOR protein because they have been shown to be inhibited by rapamycin. They include the expression of matrix-degrading metalloproteinases (MMP), tumor necrosis factor-α (TNF-α), and p53. Rapamycin significantly suppressed the UVB-mediated increase in p70 ribosomal S6 kinase activity and the interstitial collagenase (MMP1) and stromelysin-1 (MMP3) protein levels in human dermal fibroblasts compared with UVB-irradiated control fibroblasts.[43] In vivo, topical application of rapamycin before ultraviolet exposure protected mice against suppression of the contact hypersensitivity related to TNF-α induction.[44] Yarosh et al.[45] suspect that rapamycin reduces phosphorylation of p53 after UVB, maintaining the ability of p53 to inhibit TNF-α expression. Furthermore, p53 status may intervene in the responses of cells to rapamycin. When treated with rapamycin, p53 wild-type normal cells arrest in G1 phase and maintain viability whereas p53 mutant rhabomyosarcoma cells accumulate in G1 phase and undergo apoptosis.[41]

"In Vivo" Antineoplastic Properties

The effect of rapamycin or CsA on the growth of various cancer cell lines has been studied in mice. The first authors used syngenic CT-26 adenocarcinoma cells in BALB/c mice within three tumor growth models.[46] They first injected cells intraportally simulating metastasis of colon cancer to the liver. There was a marked decrease in the metastatic area in rapamycin-treated mice compared to control mice. In contrast, CsA-treated mice had an increased tumoral area. Tumor growth was also assessed after injection in the skin and in the cecal wall. In all models, the decrease of tumor growth in rapamycin-treated mice was associated to a decrease in neovascularization and the increase of tumor growth in CsA-treated mice was obviously associated with an extensive neovascularization. Rapamycin was shown to inhibit the secretion of vascular endothelial growth factor (VEGF) in vitro and in vivo. One interesting point of this study is the assessment of different doses on tumor growth and mice survival. Rapamycin was introduced 1 week after the subcutaneous injection of tumor cells. The best antitumoral efficacy corresponded roughly to doses given in organ transplantation to prevent rejection. Other authors using murine renal cell adenocarcinoma cells of BALB/c origin[42] investigated the effect of rapamycin on tumor progression, in the presence and absence of CsA in BALB/c mice, and in cell-deficient SCID-beige mice. In the SCID-beige mice, T24 human bladder transitional cell carcinoma was also used as the tumor inoculatum. Rapamycin treatment given several days after tumor inoculation, alone or with CsA, prevented tumor growth and metastatic progression. The number of renal cancer pulmonary metastases was increased in CsA-treated mice compared to untreated mice. The survival time of mice treated with both rapamycin and CsA was higher compared with control mice, CsA-treated mice, or rapamycin-treated mice. The same authors developed a human renal cell cancer pulmonary metastasis model using human RCC 786-O as the tumor challenge and the SCID-beige mice.[47] Rapamycin reduced whereas CsA increased the number of pulmonary metastases; furthermore, circulating levels of VEGF-A and TGF-β1 were lower in the rapamycin-treated mice compared to untreated or CsA-treated mice. Unlike the first study, the combination rapamycin plus CsA did not show significantly better results compared to rapamycin.

Clinical Data on Antineoplastic Properties

The preliminary data about the incidence of skin tumors developed by patients under rapamycin concerns kidney transplant patients treated from the time of transplantation. The first results were assessed at 2 years after graft and comprised five multicenter studies enrolling a total of 1886 patients in various regimens.[48] All patients received corticosteroids. The first studies compared 2 and 5 mg rapamycin to azathioprine or placebo given in 1295 patients under CsA. An additional two trials compared rapamycin to CsA as base therapy. The last study included 430 patients who initially received 2 mg rapamycin in association with CsA; they were randomized at 3 months to remain on triple therapy ($n = 215$) or to have CsA withdrawn. The incidence of skin malignancy was lower in all groups of patients treated with rapamycin especially in the 215 patients having CsA withdrawn compared to those receiving continuous association with CsA (2.3% vs. 4.7%). It was concluded that rapamycin confers a benefit with regard to skin cancer, even when given with CsA. The incidence of other malignancies, however, appeared to be lower only when rapamycin was given as base therapy without CsA or following early CsA withdrawal. Another study also reported a lower rate of skin tumor in a cohort of 1008 patients treated with rapamycin at a single center for up to 10 years.[49] It can be speculated that patients may benefit from a switch after the occurrence of the first skin tumors because experimental data have shown that rapamycin could inhibit tumoral growth even given several days after tumor inoculation.

Rapamycin tolerance is good and its use is extending to heart and liver transplantation.[50,51] The main advantages consist of less nephrotoxicity and hypertension compared to calcineurin inhibitors. Side effects are dose-dependent and include mainly hyperlipidemia, thrombocytopenia, leucopenia, and anemia.[52] Cardiovascular risk factors do not appear to be increased with rapamycin-based compared with CsA-based therapy.[53] Dermatologic side effects comprise mouth ulcers, acne, eyelid edema,[54] lymphedema,[55] and angiedema.[56] Furthermore, wound healing and clotting problems could be related to disorders in tumor blood vessel circulation.[57,58] Recent data reported that rapamycin side effects, especially pneumopathy and proteinuria, were more frequent after switch than in the immediate posttransplant period treatment when the indication was calcineurin inhibitors nephrotoxicity.[52]

The rapamycin ester CCI-779 is being developed as an anticancer agent. Preliminary data indicate that in vitro everolimus inhibits growth of numerous tumor cell lines.[41] In vivo, one study reported its antitumor effect on subcutaneous growth of Epstein-Barr virus-positive B cells in SCID mice.[59] Currently, everolimus is used as an immunosuppressive agent only in association with CsA, and there are not yet clinical data on the cancer risk in these patients.

Conclusion

Data on the best management of immunosuppressive treatments in organ transplant patients with skin cancer are changing. New strategies are not only based on minimizing immunosuppression. There is a rationale suggesting that inhibitors of the protein mTOR could be of great interest. Although everolimus is expected to have similar antitumor properties, the most promising data are currently provided by rapamycin. The problem is to assess the most appropriate time to introduce this drug in the immunosuppressive regimen both to allow the best graft function and to prevent skin cancer in transplant patients. For each patient, the advantages and the side effects of this drug must be considered. In our opinion, switch to rapamycin should be considered for transplant patients with squamous cell carcinoma owing to the high risk of subsequent skin lesions.[60] Clinical studies are required to assess accurately the preventive effect of mTOR inhibitors on the occurrence of new skin lesion in transplant patients with skin cancer.

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