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# The effect of switching from calcineurin inhibitor to sirolimus on the incidence of skin cancers in kidney transplant recipients

*Editor*

The introduction of calcineurin inhibitors (CNI) has greatly improved average graft survival; however, they have also been responsible for an increase in the number of skin cancers in renal transplant recipients (RTR). Patients receiving cyclosporine, azathioprine, and prednisolone have a significantly (2.8 times) higher risk of cutaneous squamous cell carcinomas than those receiving azathioprine and prednisolone.[1] CNI cause blockade of apoptosis and promote the synthesis of pro-neoplastic cytokines including transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF), causing tumour metastasis and vascularization.

Sirolimus (SRL) is an inhibitor of the mammalian target of rapamycin (mTOR). It exerts its anti-neoplastic effect by suppressing TGF-α and VEGF signal transduction and thereby blocking tumour growth and angiogenesis. SRL-based regimens either with or without CNI reduce the relative risk of *de novo* malignancy.[2]

We recently studied five RTR who had been changed from CNI to SRL-based regimens because of recurrent multiple non-melanomatous skin cancers (NMSC). Four of the patients studied were treated with cyclosporine; the fifth was taking tacrolimus. At the time of switch, only one patient was taking azathioprine, and none were being treated with mycophenolate. Four of the five RTR were taking low-dose prednisolone. We compared the incidence of skin cancer per person year before and after the change. All cancers occurring before the switch were regarded as 'pre-switch'; those discovered after the switch, regardless of how soon thereafter they occurred, were considered 'post-switch'. We consider that this eliminated any possibility of an over estimation of the effect of introducing SRL.

The pre-switch time period consisted of a total of 15 patient years; the post-switch period consisted of 12.6 patient years, and there were a total of 14 NMSC occurring in the 3 years prior to conversion to SRL and 3 cancers in the subsequent 3 years. The incidence of skin cancers post-SRL switch decreased from 71.9% pre-switch to 23.8% per person year post-switch ($P = 0.0347$). The corresponding values over 3 years were 93% compared with 24% ($P = 0.0197$). This is presented graphically in Fig. 1. The mean serum creatinine was 122 mol/L before switching and 96 mol/L after switching; although this reduction did not reach statistical significance ($P = 0.4164$), it demonstrates that renal function remained stable.

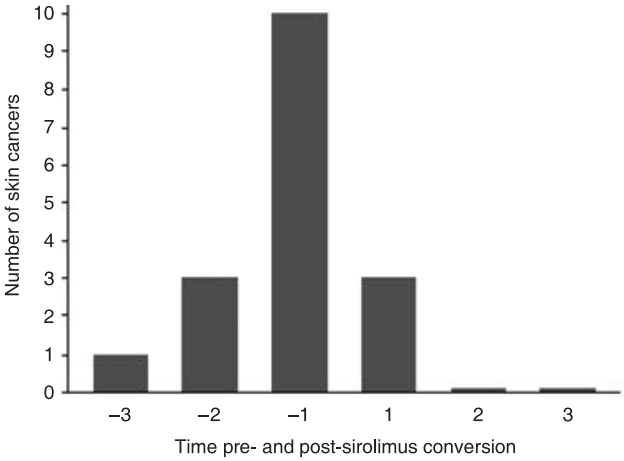


**Figure 1** Number of skin cancers before and after switch to sirolimus.

The scale of the problem represented by post-transplant skin cancers has been highlighted in recent papers. In an Irish population, NMSC occurring in RTR are responsible for 1% of the national total of these malignancies. The incidence of skin cancers in Irish RTR is 12.5%. The standardized incidence rates for invasive NMSC (33-fold increase), *in situ* cancers of the skin (65-fold increase), and squamous cell carcinomas (88-fold increase) are all significantly increased.[3] Similar rates of post-transplant NMSC are seen worldwide. While vigilant surveillance programmes to initiate prompt treatment have been successful in preventing significant mortality from these malignancies, and while the use of oral retinoids has shown promise in reducing the frequency of their occurrence, they remain a considerable cause of morbidity in the RTR. Our results show a significant reduction in the rate of skin cancers occurring in transplant patients following the substitution of SRL for CNI. Patients' renal function was not adversely affected by this switch. We feel that SRL has great promise as an alternative to CNI in patients with post-transplant skin cancers.

RF McQuillan,* CM O'Seaghdha, A Bagatto, M Manusamy, N Errakiah, C Sinnott, P O'Kelly, GM Murphy, PJ Conlon
Department of Nephrology, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland
*Correspondence: RF McQuillan. E-mail: rorymcquillan@yahoo.com

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# Lack of association between the promoter polymorphisms at positions –238 and –308 of the tumour necrosis factor alpha gene and acne vulgaris in Polish patients

*Editor*

The genetic influence on pathogenesis of acne is well documented in twins and in genealogic studies, but there are only few reports concentrated on the association between acne susceptibility and genes.[1] Tumour necrosis factor-α (TNF-α) plays an important role in the promotion of inflammatory process and in the pathogenesis of malignant, and inflammatory diseases. The mechanisms of the inflammatory stage of acne are not well understood; however, it is known that *Propionibactrium acnes* are involved in development of inflammatory lesions. *P. acnes* can induce human keratinocytes and monocytes to produce TNF-α.[2,3] Several *TNF-α* gene single nucleotide polymorphisms (SNP) have been described. The *TNF-α* gene 238 G/A and –308 G/A promoter region polymorphisms are associated with increased cytokine production.[4] There are differences described in allelic distribution of the TNF-α in various populations.[5]

The aim of our study was to find the connection between the –238 and –308 *TNF-α* gene polymorphism and the occurrence of acne.

84 patients with acne and 75 healthy controls (older than 20) without acne in anamnesis were analysed. The –238 G/A and –308 G/A polymorphism in promoter region of the TNF-α was analysed by amplification refractory mutation system-polymerase chain reaction. The result was evaluated by the $\chi^2$ test with Yates' correction.

The TNF-α genotype distribution in both groups is shown at the Table 1. There were no significant difference in genotype frequencies between patients with acne and controls.

The association between –238 and –308 *TNF-α* gene polymorphism and inflammatory or malignant disorders have been shown in various studies, but this is the first report concerning the *TNF-α* gene polymorphism and acne. Our results show lack of association between the promoter polymorphisms at positions –238 and –308 of the *TNF-α* gene and acne vulgaris in Polish patients, but it is well known that also others proinflammatory interleukins such as interleukin-1 (IL-1), IL-2, IL-8 and granulocyte-macrophage colony-stimulating factor are also involved in evolution of the inflammatory lesions.[2,3] Acne pathogenesis is a multifactorial process, and many different genes may be responsible for acne susceptibility. Paraskevaidis *et al.*[6] found the correlation between human cytochrome *P*450 1A1 (*CYP1A1*) gene polymorphism and acne, which was confirmed by our study.[7] He *et al.*[8] revealed the association of acne with CYP17.[8]

In conclusion, presented data suggest that SNP at –238 and –308 of the promoter region of the *TNF-α* gene does not play a role in acne pathogenesis; however, further investigations in larger group and different populations are required.

**Table 1.** Frequency of TNF-α –238G/A and –308G/A genotypes in patients with acne and controls

| | Controls *N* = 75 | Acne *N* = 84 |
|---|---|---|
| **TNFα 308 genotype** | | |
| GG | 49 (65.4%) | 67 (79.8%) |
| GA | 25 (33.3%) | 14 (16.6%) |
| AA | 1 (1.3%) | 3 (3.6%) |
| **Allele** | | |
| G | 123 (82%) | 148 (88.1%) |
| A | 27 (18%) | 20 (11.9%) |
| **TNFα 238 genotype** | | |
| GG | 69 (92%) | 75 (89.3%) |
| GA | 6 (8%) | 9 (10.7%) |
| AA | 0 | 0 |
| **Allele** | | |
| G | 144 (96%) | 159 (94.6%) |
| A | 6 (4%) | 9 (5.4%) |

M Sobjanek,*† M Zabłotna,† B Nedoszytko,† M Sokołowska-Wojdyło,† A Włodarkiewicz‡
†Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Poland, ‡Department of Department of Maxillofacial Surgery, Medical University of Gdańsk, Poland
*Correspondence: M Sobjanek. E-mail: sobjanek@wp.pl


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