

Prograf® (Tacrolimus) – A Cornerstone of Immunosuppressive Therapy

a report by

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Significant progress in the practice of solid organ transplantation has given new hope, and indeed life, to thousands of people all over the world. However, the problems associated with these procedures are so many and are so complex that to solve them has taken a massive research effort on the part of the medical community and pharmaceutical industry. Researchers at Fujisawa have made a notable contribution to this effort through the discovery and development of Prograf® (tacrolimus), a cornerstone immunosuppressant developed for use in solid organ transplantation.

Prograf

In 1984, Fujisawa researchers isolated an active immunosuppressant factor from the culture broth of a soil micro-organism, *Streptomyces tsukubaensis*, found near Mount Tsukuba in Japan. This active ingredient was initially code-named FK506, but subsequently given the generic name tacrolimus, and eventually the trademark registration Prograf.

Extensive *in vitro* and *in vivo* testing confirmed the marked immunosuppressive activity of tacrolimus. Although tacrolimus and ciclosporin* are structurally distinct, both agents inhibit the expression of interleukin-2 dependent T-cell

proliferation, a major mechanism in the rejection pathway. However, studies conducted in a range of animal models showed tacrolimus to effectively prevent graft rejection at doses 10 to 100 times lower than the dose of ciclosporin required in the same models.⁵

The first clinical experience with tacrolimus was gained at the University of Pittsburgh, in February 1989. Professor Starzl, the eminent transplant physician who had carried out the world's first successful liver transplant in 1967, pioneered the use of tacrolimus in patients who were experiencing liver rejection despite receiving optimal therapy with existing immunosuppressive agents. Most of the patients survived and it appeared that tacrolimus therapy, used in combination with low-dose corticosteroids, was an effective immunosuppressive regimen. Subsequently, Professor Starzl extended its use to the primary treatment of liver, kidney and heart transplant patients.

Tacrolimus in Liver Transplantation

Tacrolimus has been shown to be more effective than ciclosporin in preventing acute rejection following liver transplantation. In the large European multicentre liver study,^{6,7} the three-year data demonstrated that

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(* All references to ciclosporin refer to the original formulation of ciclosporin, except where explicitly stated.)



patients receiving tacrolimus had significantly less acute rejection compared with the ciclosporin-treated patients (45.4% versus 55.1%; $p=0.006$). In addition, the severity of rejection was greater in patients treated with ciclosporin. Tacrolimus-treated patients also had significantly less corticosteroid-resistant, refractory acute and chronic rejection. This reduction in rejection episodes was achieved despite a significantly reduced need for corticosteroid therapy. The lower use of corticosteroids is of benefit because many corticosteroid-associated adverse events can be reduced or avoided completely. The large US multicentre study showed similar findings.⁸

These data were confirmed by a meta-analysis of the three-year data from the European and US studies.⁹ As the frequency and intensity of acute rejection episodes is believed to be more strongly correlated to the subsequent development of chronic rejection than any other clinical parameter,¹⁰ these data are of special significance in terms of the long-term graft survival. Indeed, the meta-analysis results, when adjusted for protocol differences between the two studies, demonstrated that significantly more tacrolimus-treated patients were alive after three years compared with those receiving ciclosporin ($p=0.02$). The benefits associated with tacrolimus have recently been shown to be sustained when compared with the microemulsion formulation of ciclosporin.¹¹

Tacrolimus in Kidney Transplantation

Patients requiring kidney grafts represent the largest transplant group. Multicentre studies in the US and

Europe have shown that tacrolimus is effective and well tolerated as cornerstone therapy in kidney transplantation. Consistently lower acute rejection rates have been achieved with tacrolimus compared with ciclosporin and ciclosporin microemulsion-based regimens. There is now four-year data available from the European multicentre study,¹² showing that the incidence of acute rejection is lower in patients receiving tacrolimus compared with ciclosporin (25.9% versus 45.7%) while the incidence of chronic rejection is also reduced in tacrolimus-treated patients (5.5% versus 11.3%). Recent analyses of kidney transplant data further indicate that tacrolimus reduces the likelihood of acute vascular rejection compared with ciclosporin¹³ – involvement of the renal vasculature – as opposed to just the interstitial tissue, is one of the primary risk factors for chronic rejection and graft loss.¹⁴ Importantly, the efficacy of tacrolimus in terms of reducing rejection is maintained when compared with the microemulsion formulation of ciclosporin.¹⁵ The significant reduction in the incidence of acute, corticosteroid-resistant and vascular rejection achieved with tacrolimus has important long-term implications given the prognostic influence of rejection on graft survival. Indeed, five-year data from the US multicentre kidney study reveals a significant difference in graft survival rates between tacrolimus- and ciclosporin-treated patients (when combining patients crossing over to tacrolimus for refractory rejection with patients losing their grafts).¹⁶

Importantly, tacrolimus is capable of salvaging grafts that are experiencing rejection after ciclosporin treatment.^{17,18} Despite these advances in transplantation and immuno-suppression, there is a critical shortage of

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donor organs across the world. It is therefore crucial that optimal immuno-suppressive therapy is used to prevent graft rejection and potential graft loss.

Tacrolimus – Added Benefits

Tacrolimus also has other benefits besides a reduction in acute rejection. Patients receiving tacrolimus require less concomitant corticosteroid therapy such as prednisolone.⁹ This is important not only in adults but particularly in younger patients to reduce the risk of corticosteroid-linked side effects such as growth retardation, obesity and skin problems.¹⁹ Tacrolimus also does not produce the more distressing side effects associated with ciclosporin treatment, for example, excessive facial hair growth and gum hyperplasia.^{20,21} Lower levels of blood lipids and reduced need for antihypertensive agents have also been observed in patients receiving tacrolimu. Potentially, patients reduce the risk of cardiovascular complications.

Tacrolimus Worldwide

Tacrolimus was first launched in Japan in 1993 initiating a new era in maintenance

immunosuppression. In 1994 it was introduced in the US as primary therapy in liver transplant patients, and in the UK as primary therapy in liver and kidney transplant patients. Further launches have followed in major markets and, to date, tacrolimus is commercially available in approximately 40 countries worldwide. Manufactured in bulk form in Japan, tacrolimus is formulated and packaged by Fujisawa Ireland from where it is shipped direct to world markets. Tacrolimus can be taken orally immediately post-transplantation in the majority of cases and is available in 0.5mg, 1mg and 5mg capsules, as well as in a concentrate for infusion (5mg/mL). ■

Contact Information

Additional information on Fujisawa GmbH can be found on the Company's website:

www.fujisawaeurope.com

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