Summary of Results for Laypersons

What was the Study Called?

Prograf® (tacrolimus) as Secondary Intervention vs. Continuation of Cyclosporine in Patients at Risk for Chronic Renal Allograft Failure

Why was this Study Needed?

The immune system is part of the body that fights foreign objects or infections. After organ transplantation, the immune system recognizes the new organ as a foreign object. Before this study started, cyclosporine was usually used to reduce the strength of the immune system in patients with a transplant. Cyclosporine (also known as Neoral, Sandimmune, Restasis and Gengraf) prevented the body from rejecting kidney transplants in most of patients in the short term. But by 8 to 10 years after transplantation, more than half of the patients lost their kidney transplants. There was a need for studying new medicines such as tacrolimus (also known as FK506, immediate-release tacrolimus, Prograf, Modigraf, Adoport, Capexion, Vivadex, Tacni, Tacniteva and Tacni-transplant).

This study was conducted in patients who received a kidney transplant. The patients took cyclosporine to prevent their body from rejecting their kidney transplant. They were at risk for kidney failure. About one-third of the patients continued to take cyclosporine. The other patients took tacrolimus instead.

The main question this study helped answer was did tacrolimus help the kidney transplant survive longer than cyclosporine did. It was also important to find out what unwanted effects these patients had from the study medicines.

This study took place at 15 clinics in Canada. The study took place from April 1999 to February 2006. When the study ended, the sponsor (Astellas) reviewed all the study information and created a report of the results. This is a summary of that report.

What Kind of Study was This and Who Took Part in it?

This was an "open-label" study. This means that all patients knew which of the 2 study medicines they were taking, tacrolimus or cyclosporine.

Patients could take part in the study if:

- They had received a kidney transplant.
- They were at least 12 years old when they received their kidney transplant.
- They had received their kidney transplant at least 3 months before study start.
- They had been taking cyclosporine ever since they received their kidney transplant.
- They were considered to be at risk for kidney failure because of the poor working condition of their kidney transplant.
- A piece of tissue (biopsy) was taken from their kidney transplant to check it for damage or disease. The working condition of their kidney transplant was poor during the week that the biopsy was taken.

Patients could not take part in the study if:

- They had received a transplant of an organ that was not a kidney.
- They needed a treatment called "dialysis" to filter out wastes and extra salt and fluid from the blood. The kidneys normally do this filtering.
- They had new kidney disease or their original kidney disease had come back.
- Their result on a creatinine test was lower than the value that was specified in the study protocol. That predicted that their kidneys worked poorly in removing creatinine from the blood.
- Within 3 months before study start, they changed the treatment that reduced the strength of their immune system. This was also the treatment that helped prevent their body from rejecting their kidney transplant.
- Blood vessels were inflamed in the biopsy taken from their kidney transplant within 6 months before study start. This was a sign of rejection of the kidney transplant by the body.

During this study, the study doctor did a check-up of the patients at 8 study visits. At visit 1, patients were checked to see if they could be in the study. Patients who could be in the study were picked for 1 of 2 treatments by chance alone:

- Cyclosporine: Patients picked for cyclosporine continued to take cyclosporine. If needed, the study doctor adjusted the dose to get the right amount of cyclosporine in the blood.
- Tacrolimus: Patients picked for tacrolimus stopped taking cyclosporine. Within 1 day after their last dose of cyclosporine, they took 2 doses of tacrolimus per day. Their total daily dose was 0.3 mg per day per kg body weight or $1/50^{th}$ of their last cyclosporine dose, whichever was less. Thereafter, the study doctor adjusted the dose to get the right amount of tacrolimus in the blood.

Twice as many patients were picked for tacrolimus as for cyclosporine.

Visits 2 through 5 were every 6 months. Visits 6 through 8 were every 12 months. To check for damage or disease, biopsies from the patients' kidney transplant were taken. The biopsy was taken within 6 months before study start. The biopsy was also taken after the patients had taken study medicines for 18 and 36 months. The last visit (visit 8) was after patients took study medicines for 60 months (5 years).

A total of 106 patients were in this study and received at least 1 dose of study medicine:

- A total of 36 patients continued to take cyclosporin.
- A total of 70 patients took tacrolimus.

	Number of Patients	
	Tacrolimus (out of 70 patients)	**Cyclosporine (out of 36 patients)**
Age Group		
Aged 20 to 74 years	70	36
Sex		
Men	49	29
Women	21	7
Clinic Location		
European Union Countries	0	0
Outside European Union	70	36
Canada	70	36

What Were the Study Results?

This study was conducted in patients who received a kidney transplant. They took cyclosporine and were at risk of losing their kidney transplant. About one-third of the patients continued to take cyclosporine. The other patients took tacrolimus instead. The study looked at the survival of the kidney transplant.

Of the patients who continued to take cyclosporine, 19.4% lost their kidney transplant over 5 years. Of the patients who took tacrolimus, 27.1% lost their kidney transplant over 5 years.

The study was planned for 450 patients, but only 106 patients took part. There were not enough patients to determine which of the 2 study medicines helped kidney transplants survive longer.

What Adverse Reactions did Patients Have?

A lot of research is needed to know whether a medicine causes a medical problem. So when new medicines are being studied researchers keep track of all medical problems that patients have while they are in the study. These medical problems are called “adverse events” and are recorded whether or not they might be caused by the treatment taken. An “adverse reaction” is any medical problem or “adverse event” that is judged by the study doctor to be possibly caused by a medicine or treatment used in the study.

Tacrolimus and cyclosporine have been tested in many patient studies. Thus, the types of adverse events that these study medicines cause are well known.

In this study, the researchers kept track only of adverse events that were thought to have an effect on the survival of kidney transplants. They did not record which adverse events were judged by the study doctor to be possibly caused by the study medicines. The researchers did record for which adverse events patients were treated during the study.

The table below shows the most common adverse events for which patients were treated by the end of the study (60 months). More patients in the cyclosporine group than in the tacrolimus group were treated for issues that could damage the heart muscle. The number of patients who were treated for other adverse events was similar between the 2 groups.

Adverse Event that Patients Were Treated for	Tacrolimus (out of 70 patients)	Cyclosporine (out of 36 patients)
High blood pressure	39 (55.7%)	25 (69.4%)
High blood levels of fatty substances	26 (37.1%)	19 (52.8%)
Any issues that could damage the heart muscle	5 (7.1%)	10 (27.8%)
Disease in which the body does not make or use insulin well, resulting in blood sugar level that is too high (diabetes)	8 (11.4%)	5 (13.9%)
Increased blood sugar level	4 (5.7%)	1 (2.8%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care. None of the patients experienced serious adverse reactions.

Nine patients died during the study. None of the patients died because of the study medicines.

Where Can I Learn More About This Study?

Astellas may perform additional studies to better understand tacrolimus.

This summary of the clinical study results is available online at http://www.astellasclinicalstudyresults.com.

Please remember that researchers look at the results of many studies to find out how well medicines work and which adverse reactions they might cause. If you have questions about tacrolimus, please discuss these with your doctor.

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