Summary of Results for Laypersons

What was the Study Called?

A Two Centre Clinical Pilot Study in Children With Tacrolimus (FK506) Fine Granule Formulation As Immunosuppressive Therapy in Liver Allograft Transplantation

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. A combination of tacrolimus with another medicine is usually used to reduce the strength of the immune system in patients with a transplant. The other medicine could be tacrolimus or azathioprine. The medicine combination prevents the body from rejecting organ transplants. Before this study started, tacrolimus capsules were the approved formulation to use in combination with corticosteroids. Capsules are difficult for children to swallow. Therefore, there was a need to study a tacrolimus formulation that was easier to use in children. Tacrolimus granules (also known as Modigraf or Prograf granules) come in packets. Before use, the granules need be stirred in water until they have been suspended completely. This type of solution is easy to swallow by children.

This study was conducted in children who had received a liver transplant. The children took tacrolimus granules with a low dose of corticosteroids and azathioprine for 1 year.

The study answered the question of how effective the tacrolimus granules formulation was in helping liver transplants survive for 1 year. The study looked at patients who had transplant rejection by the body at 1 year. The study also looked at the survival of patients and transplants at 1 year. It was also important to find out what unwanted effects these patients had from the tacrolimus granules.

This study took place at 2 clinics, 1 in Belgium and 1 in France. The study started in March 1996 and ended in July 1998. 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 that they took tacrolimus granules. They also knew that they took a low dose of corticosteroids and azathioprine. The doctors and medical staff also knew what study treatment the patients took.

Children could take part in the study if:

- They had received a liver transplant.
- They were not older than 15 years.

Patients could not take part in the study if:

- They had received a liver transplant in the past.
- They had received other organ transplants in the past or they had received a transplant of more than 1 organ in the past.

- Patients had cancer or had cancer in the past.
- Their kidneys did not work well.
- They had a liver transplant from a donor with a different blood type than their own. This could cause their immune system to reject the transplant.
- They had a serious liver infection that affected tissues outside the liver. And they did not receive appropriate treatment for the liver infection.

During the study, the study doctor did a check-up of the patients at 14 study visits. Visit 1 was held the day that the skin was closed after the transplant surgery. At this visit, the patients were checked to see if they could be in the study. Patients who could be in the study received the study treatment. The study treatment was tacrolimus granules with a low dose of corticosteroids and azathioprine.

- Tacrolimus granules: The planned initial daily dose after surgery was tacrolimus via infusion in a vein (0.045 mg/kg per 24 hours) for 12 hours to 4 days. Patients were to start tacrolimus treatment as soon as possible after surgery but no more than 6 hours after the skin was closed. No sooner than 12 hours after the infusion was stopped, patients were to take tacrolimus granules by mouth (0.3 mg/kg twice daily). The study doctor adjusted the dose to get the right amount of tacrolimus in the blood.
- Corticosteroids: Patients were to receive corticosteroids according to standard practice at their clinic.
- Azathioprine: Patients were to receive azathioprine according to the practice at their clinic.

Visits 2 through 7 were at days 1, 5, 9, 14, 21 and 28. Study visits 8 through 11 were at weeks 6, 8, 10 and 12. Study visits 12 through 14 were at months 6, 9 and 12. At each visit, the study doctor met with the patient to evaluate their health as well as assess the safety and effectiveness of the treatment. The clinic staff took blood samples to check the amount of tacrolimus in the blood. The study doctor adjusted the dose of study treatment based on the specific needs of the patient.

A total of 28 patients were in the study and took at least 1 dose of tacrolimus granules.

	Tacrolimus Granules (out of 28 patients)
Age Group	
Aged 0 to less than 5 years	18
Aged 5 to 13 years	10
Sex	
Boys	13
Girls	15
Clinic Location	
European Union Countries	28
Belgium	15
France	13
Outside European Union	0

What Were the Study Results?

This study was conducted in children who had received a liver transplant. The study looked at patients who had transplant rejection by the body during the 1-year study. The study also looked at the survival of patients and transplants at 1 year.

The study found that 6 (21.4%) patients who took tacrolimus granules had features of transplant rejection during the 1-year study. Graft and patient survival rates were 89.3% at 1 year because of the death of 3 patients (and thus the loss of 3 liver transplants).

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.

The table below shows the most common adverse reactions experienced by patients who took at least 1 dose of study treatment.

Adverse Reaction	Tacrolimus Granules (out of 28 patients)
High blood pressure	12 (42.9%)
Fever	10 (35.7%)
Infection	7 (25.0%)
Diarrhea	7 (25.0%)
Increased blood level of uric acid, a waste material from food digestion	6 (21.4%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care.

The table below shows the most common serious adverse reactions.

Serious adverse Reaction	Tacrolimus Granules (out of 28 patients)
Infection	2 (7.1%)
Increased blood level of a liver enzyme (aspartate aminotransferase)	2 (7.1%)
Increased blood level of a liver enzyme (alanine aminotransferase)	2 (7.1%)
Increased blood level of a liver enzyme (gamma-glutamyl transferase)	2 (7.1%)

Two patients died while on study treatment (tacrolimus granules). The death of 1 of the 2 patients could have been related to the tacrolimus granules. This patient experienced a serious adverse reaction of increased blood level of potassium.

A third patient died during the study after stopping study treatment (tacrolimus granules). This death could have been related to the tacrolimus granules. This patient experienced a serious adverse reaction of infiltration of immune system cells that looks like a lymphoma but is not cancerous.

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.

Sponsor contact details:

Astellas Pharma Global Development (formerly Fujisawa GmbH)
1 Astellas Way
Northbrook, IL 60062
USA