# Summary of Results for Laypersons

## What was the Study Called?

An Open, Randomised, Comparative, Multicentre Paediatric Clinical Trial Comparing the Efficacy and Safety of a Dual Regimen With Oral Tacrolimus (FK506) Versus a Triple Regimen With Oral Cyclosporin-Microemulsion in Primary 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 and another medicine is usually used to reduce the strength of the immune system in patients with a transplant. The other medicine could be corticosteroids 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 to 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. One group of the children took tacrolimus granules with a low dose of corticosteroids for 1 year. The other group took cyclosporine microemulsion with a low dose of corticosteroids and azathioprine for 1 year.

The study answered the question how effective tacrolimus granules were compared to cyclosporine microemulsion in helping liver transplants survive for 1 year. The study looked at patients who had transplant rejection by the body during the 1-year study. The study also compared the rejection rates of these patients over 1 year between the 2 treatments. It was also important to find out what unwanted effects these patients had from the study treatments.

This study took place at 10 clinics in Belgium, France, Germany, Italy, Spain and the UK. The study started in June 1997 and ended in December 2000. 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 study treatment they took, tacrolimus granules or cyclosporine microemulsion. They also knew that they took a low dose of corticosteroids. Patients who took cyclosporine microemulsion knew that they also took 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 16 years. They weighed no more than 40 kg.

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. It was acceptable for patients to have liver cancer that had not spread in the body.
- There was a medical reason for them not to take azathioprine.
- 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 an infection in their bloodstream that required treatment at the beginning of the study.

During the study, the study doctor did a check-up of the patients at 14 study visits. Visit 1 was held the day of the patient's liver 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 were picked for 1 of 2 treatments (tacrolimus granules or cyclosporine microemulsion) by chance alone:

- Tacrolimus granules with a low dose of corticosteroids
  *Tacrolimus granules*: The planned initial daily dose after surgery was 0.15 mg/kg twice daily taken by mouth (orally). Patients were to take the first dose as soon as possible after surgery but no more than 6 hours after the skin was closed. (This could be up to 24 hours after the skin was closed in case of kidney problems.) After the initial dose, the study doctor was allowed to adjust the dose to get the right amount of tacrolimus in the blood.
  *Corticosteroids*: Patients received methylprednisolone (10 mg/kg) via an infusion into a vein during surgery. After the surgery, patients received methylprednisolone in a vein on days 1 to 6 (2 mg/kg per day) and thereafter took oral prednisolone once daily. The dose of prednisolone was 1 mg/kg on days 7 to 13, 0.75 mg/kg on days 14 to 20, 0.5 mg/kg on days 21 to 28 and 0.25 mg/kg at months 2 to 3. Thereafter, patients took prednisolone every other day and/or tapered it off according to the practice at their clinic.

- Cyclosporine microemulsion with a low dose of corticosteroids and azathioprine
  *Cyclosporine microemulsion*: The planned initial daily dose for cyclosporine microemulsion was 5 mg/kg taken orally twice daily. Patients were to take the first dose as soon as possible after surgery but no more than 6 hours after the skin was closed. (This could be up to 24 hours after the skin was closed in case of kidney problems.) After the initial dose, the study doctor was allowed to adjust the dose to get the right amount of cyclosporine in the blood.
  *Corticosteroids*: Patients in the cyclosporine microemulsion group took the same doses of methylprednisolone and prednisolone as patients in the tacrolimus granules group.

*Azathioprine*: Patients were to take azathioprine (1.5 mg/kg) once daily for the first 3 months. Thereafter they took the dose 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 or cyclosporine in the blood. The study doctor adjusted the dose of study treatment based on the specific needs of the patient.

A total of 185 patients were in the study. A total of 181 patients took at least 1 dose of study treatment.

- 91 patients took tacrolimus granules.
- 90 patients took cyclosporine microemulsion.

| | **Tacrolimus Granules (out of 91 patients)** | **Cyclosporine Microemulsion (out of 90 patients)** |
|---|---|---|
| **Age Group** | | |
| Aged 0 to less than 5 years | 70 | 70 |
| Aged 5 to 16 years | 21 | 20 |
| **Sex** | | |
| Boys | 46 | 48 |
| Girls | 45 | 42 |
| **Clinic Location** | | |
| European Union Countries | 91 | 90 |
| Belgium | 10 | 11 |
| France | 13 | 14 |
| Germany | 27 | 25 |
| Italy | 6 | 7 |
| Spain | 18 | 17 |
| The UK | 19 | 18 |
| Outside European Union | 0 | 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 compared the rejection rates of these patients over 1 year between the 2 treatments (tacrolimus granules and cyclosporine microemulsion).

The study found that the rejection rate was lower with tacrolimus granules than with cyclosporine microemulsion. Of the patients who took tacrolimus granules, 44.5% had transplant rejection by the body during the 1-year study. Of the patients who took cyclosporine microemulsion, 59.8% had transplant rejection by the body during the 1-year study.

**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.

More patients in the tacrolimus granules group than in the cyclosporine microemulsion group had an infection with the Epstein-Barr virus. Patients in the cyclosporine microemulsion group had excess body hair where normally not present (such as beard, moustache, chest or stomach hair). None of the patients in the tacrolimus granules group had this adverse reaction.

| | **Number of Patients** | |
|---|---|---|
| **Adverse Reaction** | **Tacrolimus Granules (out of 91 patients)** | **Cyclosporine Microemulsion (out of 90 patients)** |
| Fever | 30 (33.0%) | 32 (35.6%) |
| Infection with the cytomegalovirus | 13 (14.3%) | 21 (23.3%) |
| Infection | 16 (17.6%) | 17 (18.9%) |
| Infection with the Epstein-Barr virus | 23 (25.3%) | 9 (10.0%) |
| Severe illness in which the bloodstream is overwhelmed by bacteria | 13 (14.3%) | 14 (15.6%) |
| High blood pressure | 30 (33.0%) | 37 (41.1%) |
| Higher than normal blood levels of a liver enzyme (increased blood levels of liver enzymes indicate that liver cells are damaged) | 27 (29.7%) | 21 (23.3%) |
| Diarrhea | 13 (14.3%) | 12 (13.3%) |
| Decreased blood level of magnesium | 33 (36.3%) | 23 (25.6%) |
| More acid than normal in the blood | 14 (15.4%) | 3 (3.3%) |
| Increased blood level of potassium | 10 (11.0%) | 7 (7.8%) |
| Excess body hair in children where normally not present (such as beard, moustache, chest or stomach hair) | 0 | 24 (26.7%) |
| Kidneys not working well | 10 (11.0%) | 11 (12.2%) |

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 | Number of Patients | |
|---|---|---|
| | Tacrolimus Granules (out of 91 patients) | Cyclosporine Microemulsion (out of 90 patients) |
| Fever | 18 (19.8%) | 17 (18.9%) |
| Infection with the cytomegalovirus | 4 (4.4%) | 11 (12.2%) |
| Severe illness in which the bloodstream is overwhelmed by bacteria | 7 (7.7%) | 8 (8.9%) |
| Infection with the Epstein-Barr virus | 6 (6.6%) | 2 (2.2%) |
| Higher than normal blood levels of a liver enzyme (increased blood levels of liver enzymes indicate that liver cells are damaged) | 13 (14.3%) | 11 (12.2%) |
| Diarrhea | 6 (6.6%) | 5 (5.6%) |
| Stomach flu | 6 (6.6%) | 1 (1.1%) |

A total of 16 patients died during the study.

Five patients (2 in the tacrolimus granules group and 3 in the cyclosporine microemulsion group) died while on study treatment. The death of 2 patients (1 in the tacrolimus granules group and 1 in the cyclosporine microemulsion group) could have been related to their study treatment. These patients experienced serious adverse reactions of severe illness in which the bloodstream is overwhelmed by bacteria.

Eleven patients (5 in the tacrolimus granules group and 6 in the cyclosporine microemulsion group) died during the study after they stopped taking study treatment. The death of 1 patient (cyclosporine microemulsion) could have been related to the patient's study treatment. This patient experienced a serious adverse reaction of severe illness in which the bloodstream is overwhelmed by bacteria. For 5 of the 11 patients (2 in the tacrolimus granules group and 3 in the cyclosporine microemulsion group), the study doctor did not know whether their deaths were related to their study treatments.

**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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