Summary of Results for Laypersons

What was the Study Called?

A phase IV, randomized, open-label, comparative, single-center study to assess the pharmacokinetics, safety and efficacy of Advagraf (Modified Release Tacrolimus) and Prograf (Tacrolimus) in *de novo* living donor liver transplants recipients

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. Tacrolimus is a medicine that reduces the strength of the immune system. It prevents the body from rejecting organ transplants. Tacrolimus comes in capsules to be taken by mouth (orally). Prograf (also known as FK506, immediate-release tacrolimus, Adoport, Capexion, Vivadex, Tacni, Tacniteva and Tacni-transplant) capsules are taken twice a day. Advagraf (also known as Graceptor, tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL, FK506E, MR4 or tacrolimus modified-release) capsules are easier for patients because they are taken once a day. Over 24 hours, blood levels of tacrolimus need to stay high enough to prevent transplant rejection.

There was a need to study the 2 treatments and compare the amount of tacrolimus that reached the blood over 24 hours.

The patients in this study had received a liver transplant followed by 4 days of Prograf given as an infusion. All patients then switched to taking oral tacrolimus capsules. Half of the patients took Advagraf capsules once a day. The other half took Prograf capsules twice a day. This study looked at the amount of tacrolimus that reached the blood over 24 hours on days 1 and 17 after the start of oral tacrolimus capsules. This study answered the question if that amount was the same in patients who took Advagraf and in those who took Prograf. It was also important to find out what unwanted effects these patients had from the study medicines.

This study took place at 1 clinic in South Korea. The study took place from April 2011 to May 2014. 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 took, Prograf or Advagraf.

Men and women could take part in the study if:

- They were at least 20 years old.
- They received a liver transplant from a living donor. The patients did not have antibodies against their donor's blood type.
- They received their first dose of tacrolimus and corticosteroids after the transplantation. They were expected to need tacrolimus during the entire study.

- Women were not pregnant at study start. They did not plan to become pregnant during the study. Women who could have children used reliable birth control methods during the study.

Patients could not take part in the study if:

- They had received another organ transplant in the past. They received more than 1 organ transplant, including a repeated liver transplantation.
- During the surgery, part or all of their own liver was kept. Or the patients received an artificial liver instead of a liver transplant.
- They were allergic to protocol-specified antibiotics or to tacrolimus.
- Before the transplantation, they needed treatment to reduce the strength of the immune system. (A low dose was allowed as long as patients stopped taking it just before the transplantation.) Or before the transplantation, patients needed anticancer medicines that were given to them via a vein or the mouth.
- They had or used to have cancer, unless the cancer started in the liver or skin and was cured.
- They had an infection throughout their body for which they needed treatment. The exception was disorder of the liver caused by a virus.

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:

- Advagraf: Patients received Prograf therapy (0.025 to 0.05 mg per kg body weight per day) as an infusion for 4 days. The patients then switched to oral Advagraf capsules. The first dose of Advagraf capsules was 6 times the Prograf dose given as an infusion on day 4. Thereafter, the patients took Advagraf capsules once a day.
- Prograf: Patients received Prograf therapy (0.025 to 0.05 mg per kg body weight per day) as an infusion for 4 days. The patients then switched to oral Prograf capsules. The first dose of Prograf capsules was 4 times the Prograf dose given as an infusion on day 4. Thereafter, the patients took Prograf capsules twice a day.

Visits 2 and 3 were 1 and 6 days after the start of study treatment, respectively. Visits 4, 5, 6 and 7 were 2, 3, 4 and 12 weeks after the start of study treatment, respectively. The last visit (visit 8) was after 24 weeks of study treatment. At all visits, the study doctor did a check-up. On visit 3 (second day of capsules) and visit 5 (17 days of capsules), the study doctor took a total of 10 blood samples. The study doctor took 1 sample right before the patients took their morning dose. During the 24 hours after the morning dose, the study doctor took the other samples.

A total of 100 patients were in this study and received at least 1 dose of study medicine.

- 50 patients took Advagraf.
- 50 patients took Prograf.

	Number of Patients	
	Advagraf (out of 50 patients)	**Prograf (out of 50 patients)**
Age Group		
Aged 34 to 69 years	50	50
Sex		
Men	46	38
Women	4	12
Clinic Location		
European Union Countries	0	0
Outside European Union	50	50
South Korea	50	50

What Were the Study Results?

The patients in this study had received a liver transplant followed by 4 days of Prograf infusions. All patients then switched to taking tacrolimus capsules. Half of the patients took Advagraf capsules once a day. The other half took Prograf capsules twice a day. This study looked at the amount of tacrolimus that reached the blood over 24 hours on days 1 and 17 after the start of oral tacrolimus capsules. This study compared that amount between patients who took Advagraf and those who took Prograf.

In this study, the average total daily dose of Advagraf was about 40% higher than that of Prograf. The study first looked at the amount of tacrolimus that reached the blood over 24 hours on day 1 after the start of oral tacrolimus capsules. That amount was about 269 in patients who took Advagraf and was about 275 in patients who took Prograf. This result showed that the amount of tacrolimus in the blood with the higher Advagraf dose was similar to that with Prograf. The amount of tacrolimus that reached the blood over 24 hours was also calculated for the oral dose per kg body weight. That amount was about 40% lower in patients who took Advagraf than in patients who took Prograf.

The study next looked at the amount of tacrolimus that reached the blood over 24 hours on day 17 after the start of oral tacrolimus capsules. That amount was about 323 in patients who took Advagraf and was about 253 in patients who took Prograf. This result showed that Advagraf was not much worse or better than Prograf. The amount of tacrolimus that reached the blood over 24 hours was also calculated for the oral dose per kg body weight. That amount was about 25% lower in patients who took Advagraf than in patients who took Prograf.

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 received at least 1 dose of study medicine.

More patients in the Advagraf group than in the Prograf group had increased blood level of liver enzyme. Each of the other common adverse reactions was experienced by a similar number of patients in the Advagraf and Prograf groups.

Adverse Reaction	Number of Patients	
	Advagraf (out of 47 patients)	Prograf (out of 48 patients)
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	13 (27.7%)	12 (25.0%)
Increased blood level of liver enzyme	12 (25.5%)	5 (10.4%)
Increased blood level of potassium	12 (25.5%)	14 (29.2%)
Increased blood level of fat	2 (4.3%)	3 (6.3%)
Headache or head pain	3 (6.4%)	6 (12.5%)
Numbness	3 (6.4%)	3 (6.3%)
High blood pressure	4 (8.5%)	4 (8.3%)

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

Three patients in the Advagraf group and 2 patients in the Prograf group experienced serious adverse reactions. The table below shows these serious adverse reactions.

Serious Adverse Reaction	Number of Patients	
	Advagraf (out of 47 patients)	Prograf (out of 48 patients)
Inflammation (swelling and redness) of the stomach lining caused by a common virus (cytomegalovirus)	1 (2.1%)	0
Shingles (painful rash with blisters that break open and crust over, caused by chickenpox [herpes zoster] virus)	1 (2.1%)	0
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	1 (2.1%)	0
Inflammation (swelling and redness) of the small bowel caused by a common virus (cytomegalovirus)	0	1 (2.1%)
Belly pain	0	1 (2.1%)

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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