Summary of Results for Laypersons

What was the Study Called?

A Multi-center, Randomized, Open-label, Pilot and Exploratory Study Investigating Safety and Efficacy in OPTIMIZEd Dosing of Advagraf® Kidney Transplantation in Asia. This is also known as the OPTIMIZE study.

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 corticosteroids and other medicines are usually used to reduce the strength of the immune system in patients with a transplant. The other medicines could be mycophenolate mofetil (also known as Cellcept® or MMF), Basiliximab (also known as Simulect®) and Advagraf (also known as Graceptor®, tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL®, FK506E, MR4 or tacrolimus modified-release). The medicine combination prevents the body from rejecting organ transplants.

The prescribing information for Advagraf in Korea and Taiwan states that the initial dosage is to be 0.2 to 0.3 mg per kg of body weight. The dose can be adjusted based on a patient's symptoms and guided by the patient's blood concentration of tacrolimus right before the next dose of Advagraf ("trough level of tacrolimus"). Lower doses of Advagraf have not been studied in patients with kidney transplants. Therefore, there was a need to study lower doses of Advagraf in patients with kidney transplants. Lower doses of Advagraf lead to lower trough levels of tacrolimus. The main question this study helped answer was did the kidney work differently after a lower trough level of tacrolimus. To assess kidney function, the study looked at the change in estimated glomerular filtration rate (eGFR). The eGFR is a blood test that looks at how well your kidneys are functioning.

Since most of the Advagraf studies have been conducted in Western countries, there was also a need to study Advagraf in Asian patients. It was also important to find out what unwanted effects these patients had from Advagraf.

This study took place at 6 clinics in South Korea and Taiwan. The study started in June 2014 and ended in December 2016. 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. All patients knew that they were taking Advagraf.

Men and women aged 20 to 65 years could take part in the study if:

- They had end stage kidney disease and were eligible for a kidney transplant.
- They had a kidney transplant from a living or deceased donor with a compatible blood type.
- Female patients were not pregnant.
- Female patients who might become pregnant used reliable birth control methods.

- Male patients agreed to use reliable birth control methods.

Patients could not take part in the study if:

- They had received a transplant of an organ that was not a kidney.
- Their liver did not work well. They had increased blood levels of a liver enzyme (alanine aminotransferase or aspartate aminotransferase) at least 2 times the normal level. Increased blood levels of these liver enzymes indicate that liver cells are damaged.
- They were taking medicines to reduce the strength of the immune system and prevent transplant rejection.
- They had a medical condition that could interfere with the study outcome.
- The patient was infected with the human immunodeficiency virus (HIV).
- The donor was infected with the hepatitis B virus or hepatitis C virus.

During the study, the study doctor did a check-up of the patients at each of the 12 study visits. At visit 1, patients were checked to see if they could be in the study. Within 24 hours before their kidney transplant surgery, patients received their first dose (0.2 to 0.3 mg per kg of body weight) of Advagraf. Two hours before surgery, patients were also given a 20-mg dose of basiliximab. After their kidney transplant surgery, patients received their second dose (0.2 to 0.3 mg per kg of body weight) of Advagraf. Blood samples were taken to measure the trough level of tacrolimus. On day 4, patients were given a 20-mg dose of basiliximab. Patients continued their prescribed dose of Advagraf once a day for 4 weeks to keep their trough level of tacrolimus between 6 to 10 ng/mL.

At week 4, patients were checked to see if they could remain in the study. Patients could not remain in the study if:

- They did not receive basiliximab at the time of the transplant surgery.
- The transplanted kidney was without blood supply for longer than 24 hours.
- They required more than 1 dialysis treatment in the first week after the transplant.
- They had received an organ from a donor with the exact same immune system markers.

Patients were assigned by chance alone to 1 of the following 2 treatment groups:

- Optimized dose group: Patients took an optimized dose of Advagraf once a day to keep their trough level of tacrolimus between 4 to 6 ng/mL. They continued to take this optimized dose from weeks 4 to 12. After week 12, they took a lower dose of Advagraf once a day to keep their trough level of tacrolimus between 3 to 5 ng/mL. They continued to take this dose from weeks 12 to 52.
- Standard dose group: Patients took a standard dose of Advagraf once a day to keep their trough level of tacrolimus between 6 to 10 ng/mL. They continued to take this dose from weeks 4 to 52.

At visits 2 through 12, blood samples were taken to measure the trough level of tacrolimus. Throughout the study, patients were given MMF and steroids. The dosages were based on the protocol of the study site.

A total of 66 patients were in the study and took at least 1 dose of Advagraf.

- 32 patients took the optimized dose of Advagraf.
- 34 patients took the standard dose of Advagraf.

	Number of Patients (out of 66 patients)
Age Group	
Aged 20 to 64 years	65
Aged 65 years	1
Sex	
Men	44
Women	22
Clinic Location	
South Korea	63
Taiwan	3

What Were the Study Results?

This study was conducted in adults aged 20 to 65 years who had received a kidney transplant.

The study lasted for 52 weeks. In the study, approximately half of the patients took the optimized dose of Advagraf once a day. The other half took the standard dose of Advagraf once a day. The study showed that from weeks 8 to 52, there were no differences in eGFR between the 2 treatment groups.

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 adverse reactions experienced by patients who took at least 1 dose of Advagraf.

Eleven patients in the optimized dose group and 13 patients in the standard dose group each had 1 or more adverse reactions. More patients in the optimized dose group (6 out of 32 patients [18.8%]) than in the standard dose group (3 out of 34 patients [8.8%]) experienced hair loss; the difference was 10%. There were no other notable differences between the 2 groups.

Adverse Reaction	Number of Patients	
	Optimized Dose (out of 32 patients)	Standard Dose (out of 34 patients)
Any adverse reaction	11 (34.4%)	13 (38.2%)
Inflammation of the small intestine	1 (3.1%)	0
Nausea or the urge to vomit	1 (3.1%)	0
Kidney transplant rejection (patient's body attacked the new kidney)	1 (3.1%)	0
Infection caused by the BK virus	0	1 (2.9%)
Inflammation caused by the cytomegalovirus	0	1 (2.9%)
Infection caused by the cytomegalovirus	0	2 (5.9%)
Inflammation of the nasal pathway	2 (6.3%)	1 (2.9%)
Infection caused by the herpes simplex virus	0	1 (2.9%)
Lung infection caused by *Mycobacterium tuberculosis*	1 (3.1%)	0
Urinary tract infection	0	1 (2.9%)
Intolerant effects caused by various agents	0	1 (2.9%)
Increased blood level of a liver enzyme (alanine aminotransferase)	1 (3.1%)	1 (2.9%)
Increased blood level of creatinine	1 (3.1%)	0
Increased blood level of glucose	1 (3.1%)	0
Increased blood level of uric acid	1 (3.1%)	0
Positive cytomegalovirus test	0	1 (2.9%)
Positive polyomavirus test	1 (3.1%)	0
Abnormally low urine output	1 (3.1%)	0
Type 2 diabetes	0	1 (2.9%)
Increased blood level of cholesterol	1 (1.3%)	0
Increased blood level of lipids	1 (3.1%)	1 (2.9%)
Headache or head pain	1 (3.1%)	1 (2.9%)
Hair loss	6 (18.8%)	3 (8.8%)

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

Two patients in the optimized dose group experienced serious adverse reactions. One patient experienced inflammation of the small intestine and lung infection caused by *Mycobacterium tuberculosis*. The other patient experienced kidney transplant rejection (patient's body attacked the new kidney).

Three patients in the standard dose group experienced serious adverse reactions. One patient experienced an infection caused by the cytomegalovirus. The second patient experienced a urinary tract infection. The third patient experienced inflammation caused by the cytomegalovirus. And a test showed that genetic material of the cytomegalovirus was in the blood of the third patient.

Where Can I Learn More About This Study?

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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