Multicentre, Open Label, Randomized, Two-arm, Parallel-group Study to Assess Efficacy and Safety of ENVARSUS® Compared With Tacrolimus Used as Per Current Clinical Practice in the Initial Maintenance Setting in de Novo Kidney Transplant Patients

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Primary Objective To compare tacrolimus dosing of the new Envarsus®-based immunosuppressive regimen with current clinical practice over 6 months following de novo renal transplantation in a real-life setting in different European Countries....

Ethical review	Not approved
Status	Will not start
Health condition type	Renal and urinary tract therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON44149

Source
ToetsingOnline

Brief title
Chiesi_CCD-06235AA1-01 [acronym STEADY]

Condition

- Renal and urinary tract therapeutic procedures

Synonym
Immunosuppression in recipients of primary renal transplant

Research involving
Human

Sponsors and support

Primary sponsor: Chiesi Farmaceutici
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Envarsus®, Kidney Transplant, Tacrolimus

Outcome measures

Primary outcome

Primary efficacy variable

The average tacrolimus total daily dose (TDD) from week 3 (V9) to month 6 (V15) will be compared applying an ANOVA model with treatment and country as fixed effect. Adjusted mean and adjusted mean difference will be displayed with corresponding 2-sided 95% CI.

Secondary outcome

Secondary variables:

- Tacrolimus trough level (TL);

- Ratio between TL and TDD;

- Tacrolimus total daily dose (TDD) normalized for weight (mg/kg)

- Proportion of patients with TL lower, within, or higher than the standard reference range;

- Number of dose adjustments;

- Time (days) within the standard reference range;

- Intra-patient variability of TDD and TL;

- Treatment failure rate (composite endpoint: any patient who experienced

death, graft failure, BPAR or lost to follow-up);

- Incidence of death, graft failure, BPAR, loss to follow-up;

- Time to treatment failure;

- Time to treatment discontinuation for any reason;

- Proportion of patients with delayed graft function (ie. Dialysis in the first

week);

- Proportion of patients with local diagnosis of acute rejection requiring

treatment;

- Daily dose and consumption of concomitant immunosuppressant

medications;

- BAASIS questionnaire.

Study description

Background summary

Envarsus® is a prolongedrelease formulation of tacrolimus. In Phase III studies in stable and de novo kidney transplant patients Envarsus® has already proven to be non inferior compared to twice daily tacrolimus in terms of a composite end-point of death, graft failure, acute rejection. Moreover Envarsus® is associated with a more rapid achievement of target trough levels, with more constant levels and fewer dose adjustments needed over the first year post-transplantation.

Study objective

Primary Objective
To compare tacrolimus dosing of the new Envarsus®-based immunosuppressive regimen with current clinical practice over 6 months following de novo renal transplantation in a real-life setting in different European Countries.

Secondary Objectives
- To evaluate the efficacy, safety and tolerability of the study treatments in terms of additional pharmacokinetic parameters and of clinical outcome

measures.

- To describe the current tacrolimus-based immunosuppressive strategies for renal transplantation as for local clinical practice in different European Countries.

Study design

A Multicentre, Open label, Randomized, Two-arm, parallel-group study of Envarsus® compared with tacrolimus used as per current clinical practice in the initial maintenance setting in de novo kidney transplant patients.

Intervention

Envarsus® (tacrolimus) prolonged-release tablets once daily, orally, provided in 0.75, 1.0, and 4.0 mg dose strengths.
Envarsus® treatment will commence at the starting dose of 0.17 mg/kg/day within 24 h from renal graft reperfusion following transplantation; the first dose of Envarsus® cannot be administered before transplantation.
Patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months and in the range 5-10 ng/ml afterwards.

The oral formulation of tacrolimus as for the current clinical practice at each investigational Centre (i.e. Prograf or Advagraf oral formulations)

Study burden and risks

Side effects, risks and interactions

Very common side effects (may affect more than 1 in 10 people):
- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 people):
- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood

tests)
-Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare,
hallucination, mental disorders
- Fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders. Seizure in case you*ll take Prograf
- Blurred vision, increased sensitivity to light, eye disorders
- Ringing sound in your ears
- Reduced blood flow in the heart vessels, faster heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness in breath, disorders of the respiratory tissues in the lung, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms
- Stomach problems such as inflammation or ulcer causing abdominal pain or diarrhoea, bleeding in the stomach, inflammation or ulcer in the mouth, collection of fluid in the belly, vomiting, abdominal pain, indigestion, constipation, passing wind, bloating, loose stools
- Bile duct disorders, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs or back, muscle cramps
- Insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
- Insufficient function of your transplanted organ

Uncommon side effects (may affect up to 1 in 100 people):
- Changes in blood clotting, reduction in the number of all types of blood cells (seen in blood tests)
- Dehydration, inability to urinate
- Abnormal blood test results: reduced protein or sugar, increased phosphate, increase of the
enzyme lactate dehydrogenase
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Clouding of the eye lens, impaired hearing
- Irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- Blood clot in a vein of a limb, shock
- Difficulties in breathing, respiratory tract disorders, asthma
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux

of stomach content in your throat, delayed emptying of the stomach
- Inflammation of the skin, burning sensation in the sunlight
- Joint disorders
- Painful menstruation and abnormal menstrual bleeding
- Multiple organ failure, flu-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, weight loss

Rare side effects (may affect up to 1 in 1,000 people):
- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Blindness, deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Serious illness with blistering of skin, mouth, eyes and genitals; increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 people):
- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue
- Alteration of the electrical activity of your heart called "QT prolongation in case you*ll take Advagraf.

Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including tacrolimus.
Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), agranulocytosis (a severely lowered number of white blood cells) and haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown) have been reported.

Effects on ability to drive and use machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking study drugs. These effects are more frequent if you also drink alcohol.

Risks of the Blood Collection

You may have pain, swelling, or bruising around the vein where your blood is collected. You may feel dizzy or you may faint. You may get an infection at the site of needle insertion.

Risks of the ECG
Placement of the leads may cause skin irritation, redness, or burning of the skin at the site where the leads were attached. There may be minor discomfort, similar to removing a bandage, when the leads placed on your chest are removed from your skin.

Unknown Risks
The study drugs and procedures in this study may have risks that are not known at this time.
You will be told in a timely manner of new information that may affect whether you will want to continue to participate in this study.

Interactions
Well-known interactions between tacrolimus and a number of other drugs and herbal products exist. Upon such interactions, tacrolimus blood levels can be affected and result either as low as to be non-protective from immune rejection, or as high as to be toxic. Known interacting drugs are listed below:
- Antifungal medicines: ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole.
- Macrolide antibiotics: erythromycin, clarithromycin, josamycin, and rifampicin.
- HIV protease inhibitors: ritonavir, nelfinavir, saquinavir
- HCV protease inhibitors: telaprevir, boceprevir.
- Medicines for gastric ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- Antiemetics used to treat nausea and vomiting (e.g. metoclopramide).
- Cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn.
- Contraceptive pill or other hormone treatments based on ethinylestradiol, or danazol
- Calcium channel blockers such as nifedipine, nicardipine, diltiazem and verapamil, used to treat high blood pressure or cardiac arrythmia.
- Amiodarone, an anti-arrhythmic drug.
- Medicines known as *statins* used to lower lipid, cholesterol and triglycerides, blood concentrations.
- Phenytoin and phenobarbital, used to treat epilepsy.
- Corticosteroids such as prednisolone and methylprednisolone, used to treat inflammations or suppress the immune system.
- Nefazodone, used to treat depression.
- Herbal preparations containing St. John*s Wort (Hypericum perforatum).

Avoid grapefruit (also as juice) while on treatment with study drugs, since it can also affect tacrolimus blood levels.

The following drugs may worsen kidney or nervous system problems when taken together with tacrolimus:
- anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain;
- amphotericin B, used to treat fungal infections;
- antivirals (e.g. aciclovir), used to treat viral infections.

Vaccinations
Live vaccines should be avoided.

Pregnancy
For female patients, there may be unknown risks to the foetus (unborn child) linked to the study drugs, therefore, female patients of childbearing potential, must not be pregnant. Women of childbearing potential have to use during their study participation the following reliable methods of contraception:
a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
b. Hormonal contraception (implantable, injectable, patch, oral)
c. Barrier methods of contraception: condom, occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository
d. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
True abstinence is acceptable only if reflecting your preferred life style.

At the first visit a pregnancy test is to be carried out if with woman of a fertile age.

Exposure to sun
Exposure to the sun and UV (ultraviolet) light whilst taking study drugs should be limited. Appropriate protective clothing should be worn and sunscreen with the highest sun protection factor should be used.

Contacts

Public
Chiesi Farmaceutici

Via Palermo 26/A
Parma 43122
IT
Scientific
Chiesi Farmaceutici

Via Palermo 26/A

Parma 43122
IT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient's signed informed consent obtained prior to any study-related procedure;
2. Adult men and women at least 18 years of age with end-stage renal disease who are recipients of a kidney transplant from a living or deceased donor;
3. No known contraindications to the administration of tacrolimus, other macrolides and study drugs excipients;
4. Patients must agree to use a highly reliable method of birth control;
5. Donor-recipient negative cross match test, and compatible ABO blood type;
6. Able to swallow tablets and capsules.

Exclusion criteria

1. Recipient of any transplanted organ other than kidney;
2. Recipient of a previous renal transplant;
3. Recipient of a kidney from a donor after cardiac death;
4. Recipient of a kidney from an ABO incompatible donor and positive cross-match donor;
5. Current anti-HLA Panel Reactive Antibody (PRA) levels higher than 30%;
6. Recipient of a kidney with a cold ischemia time of * 30 hours;
7. White blood cells count * 2.8x109 cells/L unless ANC >1.0x109/L;
8. Platelet count < 50 x109 cells/L;

9. ALT or AST levels >3 times the normal upper limit during the 30 days prior transplant procedure;
10. Current abuse of drugs or alcohol;
11. Incapable of understanding purpose and risk of study, unable to give written informed consent or unwilling to comply with study protocol;
12. Treatment with any other investigational agent in the 30 days prior to enrolment;
13. Kidney recipients and/or donors positive for HCV (HCV-RNA positive or HCV-Ab positive respectively);
14. Kidney recipients and/or donors positive for HBV (HBV-DNA and/or HBS-Ag positive);
15. Recipients positive for HIV;
16. Patient or donor with current diagnosis or history of malignancy within the past 5 years except basal or non-metastatic squamous cell carcinoma of the skin successfully treated;
17. Uncontrolled concomitant infection, systemic infection requiring treatment or any other unstable condition that could interfere with study objectives;
18. Severe diarrhoea, vomiting, active peptic ulcer or GI disorder that may affect absorption of tacrolimus;
19. Known hypersensitivity to tacrolimus; other macrolides and study drugs excipients
20. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are willing to use one or more reliable methods of contraception.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf®
Generic name:	Tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Envarsus®
Generic name:	Tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prograf®
Generic name:	Tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	05-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014□004314□29-NL
ClinicalTrials.gov	NCT02432833
CCMO	NL54295.041.15