# Clinical trial results:
# Tratamiento con inmunoglobulinas y rituximab en el rechazo crónico humoral en el trasplante renal: estudio multicéntrico, prospectivo, randomizado y controlado con placebo.

# Treatment with intravenous immunoglobulins and rituximab in renal transplant recipients with chronic humoral rejection: a multicentre, prospective, randomized, placebo-controlled study.

## Summary

| | |
|---|---|
| EudraCT number | 2010-023746-67 |
| Trial protocol | ES |
| Global end of trial date | 30 December 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 December 2021 |
| First version publication date | 04 December 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | TRITON |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | VHIR |
| Sponsor organisation address | Passeig Vall Hebron 119-129, Barcelona, Spain, 08035 |
| Public contact | Joaquin Lopez-Soriano, VHIR, joaquin.lopez.soriano@vhir.org |
| Scientific contact | Francesc Moreso, VHIR, fjmoreso@vhebron.net |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 13 March 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of intravenous immunoglobulins (IVIG) combined with rituximab (RTX)

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and is consistent with the Principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.
Patients with proteinuria >0.5 g/day received an angiotensin converting enzyme inhibitor/angiotensin II receptor blocker.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 01 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 25 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 25 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 25 |
| From 65 to 84 years | 0 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients eligible for the study were renal transplants with biopsy-proven chronic ABMR diagnosed less than 6 months before randomization.
Other inclusion criteria were age ≥18 years, stability of renal function defined as a decrease of eGFR <15% between the time of the diagnostic biopsy and the inclusion.
1 patient withdrawed each group

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

A central blocked computerized random-generator was utilized to allocate patients to each group. Study drugs and placebo were wrapped to assure the double-blind procedure

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | IG + RTX |

Arm description:

In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

375 mg/m2 1 dose, 1 week after IG treatment

| | |
|---|---|
| Investigational medicinal product name | Immunoglobulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

0.5 g/kg intravenous, four consecutive doses every 3 weeks

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Saline 0.9% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:
The control group received an isovolumetric saline solution, following the same schedule

| **Number of subjects in period 1** | IG + RTX | Placebo |
|---|---|---|
| Started | 12 | 13 |
| Completed | 11 | 12 |
| Not completed | 1 | 1 |
| Consent withdrawn by subject | 1 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | IG + RTX |
| Reporting group description: | |
| In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose. | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | IG + RTX | Placebo | Total |
|---|---|---|---|
| Number of subjects | 12 | 13 | 25 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 47 | 49 | |
| standard deviation | ± 13 | ± 15 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 6 | 10 |
| Male | 8 | 7 | 15 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | IG + RTX |

Reporting group description:

In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description: -

### Primary: Decline of eGFR

| | |
|---|---|
| End point title | Decline of eGFR |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

One year

| End point values | IG + RTX | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 13 | | |
| Units: ml/min | | | | |
| median (standard deviation) | -4.2 (± 14.4) | -6.6 (± 12.0) | | |

### Statistical analyses

| Statistical analysis title | EGFR decline |
|---|---|
| Comparison groups | IG + RTX v Placebo |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.475 |
| Method | t-test, 2-sided |

### Secondary: Proteinuria Increase

| | |
|---|---|
| End point title | Proteinuria Increase |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

1 year

| **End point values** | IG + RTX | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 13 | | |
| Units: gram/day | | | | |
| arithmetic mean (standard error) | 0.9 (± 2.1) | 0.9 (± 2.1) | | |

**Statistical analyses**

| **Statistical analysis title** | Proteinuria |
|---|---|
| Comparison groups | IG + RTX v Placebo |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.378 |
| Method | t-test, 2-sided |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All the study

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | IG + RTX |

Reporting group description:

In the treatment group patients received four consecutive doses of intravenous immunoglobulins (IVIG) every 3 weeks and one single dose of Rituximab (RTX) 1 week after the last IVIG dose.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description: -

| Serious adverse events | IG + RTX | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 4 / 13 (30.77%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | Additional description: Acute gastroenteritis with acute renal failure | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 13 (15.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Esophagus perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary tract neoplasm | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | IG + RTX | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 12 (66.67%) | 11 / 13 (84.62%) | |
| Nervous system disorders | | | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 1 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Coagulation time abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 1 | |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pancreatic pseudocyst | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Mucus | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cold burn | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Pulmonar thromboembolism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Rash | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 1 | |
| Graft complication | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal transplant | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Adenopathy submandibular | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 13 (15.38%) | |
| occurrences (all) | 0 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Hip pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Lumbar pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Malleolar oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 13 (15.38%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 13 (23.08%) | |
| occurrences (all) | 0 | 3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The absence of any effect on circulating donor specific antibodies uggests that this treatment may also be not efficient in patients with chronic ABMR diagnosed at earlier stages

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/28949089