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