Clinical trial results:
Single-center pilot study, prospective, open-label, to evaluate the efficacy and safety of immunosuppression low nephrotoxicity, based on the use of ATeGe-Fresenius in patients with renal insufficiency pretransplant liver

Summary

EudraCT number	2011-000691-34
Trial protocol	ES
Global end of trial date	01 September 2020

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	ATG-IRA.HVH.10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01453218
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	Dra Itxarone Bilbao, Servicio de Cirugía Hepática y Trasplantes, VHIR, 0034 932746113, ibilbao@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	01 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of an immunosuppressor regimen plus induction therapy with low-dose Anti-human T-lymphocyte globulin (ATG) in preserving renal function and preventing liver rejection in liver transplantation recipients with pretransplant renal dysfunction

Protection of trial subjects:

The study was conducted in compliance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. This study was approved by the Hospital Vall d'Hebron Institutional Review Board (Barcelona, Spain). All patients provided their written informed consent form prior to initiation of the study and were allowed to withdraw at any time

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2011
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	28
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Single centre (Vall Hebron) prospective study. From January 2012 to December 2016, twenty patients received ATG as immunosuppression induction therapy. They were compared with 20 matched patients who received basiliximab immunosuppression induction therapy from January 2005 to December 2011.

Pre-assignment

Screening details:

Adult patients on the waiting list for LT from brain-dead donors with pre-LT renal dysfunction were included. In cases of cirrhosis due to hepatitis C virus (HCV) infection, negative HCV-RNA was required. Patients in the ATG study group were compared with a historical cohort of patients with pretransplant renal dysfunction

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Prospective study against historical cohort

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-T Lymphocyte Globulin

Arm description:

ATG was intravenously (i.v.) administered on Intensive Care Unit (ICU) admission at a dose of 1mg/kg/ bodyweight. All patients were premedicated with methyl prednisolone 250mg i.v., dexchlorpheniramine 5mg i.v., and paracetamol 1g. Following doses were given on days 2 and 4 with dose adjustment according to CD2/CD3 levels (>20cel/uL). The third dose of ATG on day 4 was omitted if CD2/CD3 levels were below 20 cel/uL and platelet counts <50,000cells/mm3 on the day after the second dose.

Arm type	Experimental
Investigational medicinal product name	Anti-T Lymphocyte Globulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ATG was intravenously (i.v.) administered on Intensive Care Unit (ICU) admission at a dose of 1mg/kg/ bodyweight. All patients were premedicated with methylprednisolone 250mg i.v., dexchlorpheniramine 5mg i.v., and paracetamol 1g

Arm title	Basiliximab

Arm description:

Historical cohort

Arm type	Active comparator
Investigational medicinal product name	Basiliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients in the BAS group received induction therapy with basiliximab (Simulect; Novartis) 20mg intravenously on day 0 intraoperatively afer allograf reperfusion and on day 4 afer LT.

Number of subjects in period 1	Anti-T Lymphocyte Globulin	Basiliximab
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Anti-T Lymphocyte Globulin
Reporting group description:	
ATG was intravenously (i.v.) administered on Intensive Care Unit (ICU) admission at a dose of 1mg/kg/ bodyweight. All patients were premedicated with methyl prednisolone 250mg i.v., dexchlorpheniramine 5mg i.v., and paracetamol 1g. Following doses were given on days 2 and 4 with dose adjustment according to CD2/CD3 levels (>20cel/uL). The third dose of ATG on day 4 was omitted if CD2/CD3 levels were below 20 cel/uL and platelet counts <50,000cells/mm3 on the day after the second dose.	

Reporting group title	Basiliximab
Reporting group description:	
Historical cohort	

Reporting group values	Anti-T Lymphocyte Globulin	Basiliximab	Total
Number of subjects	20	20	40
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			
arithmetic mean	60	57	
standard deviation	± 6	± 7	-
Gender categorical Units: Subjects			
Female	2	3	5
Male	18	17	35

End points

End points reporting groups

Reporting group title	Anti-T Lymphocyte Globulin
Reporting group description:	
ATG was intravenously (i.v.) administered on Intensive Care Unit (ICU) admission at a dose of 1mg/kg/ bodyweight. All patients were premedicated with methyl prednisolone 250mg i.v., dexchlorpheniramine 5mg i.v., and paracetamol 1g. Following doses were given on days 2 and 4 with dose adjustment according to CD2/CD3 levels (>20cel/uL). The third dose of ATG on day 4 was omitted if CD2/CD3 levels were below 20 cel/uL and platelet counts <50,000cells/mm3 on the day after the second dose.	

Reporting group title	Basiliximab
Reporting group description:	
Historical cohort	

Primary: ACR episodes 7 days

End point title	ACR episodes 7 days
End point description:	
Combination of absence of ACR (Acute Cellular Rejection) episodes and eGFR ≥ 60mL/min/1.73m2	
End point type	Primary
End point timeframe:	
7 days after transplantation	

End point values	Anti-T Lymphocyte Globulin	Basiliximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percent				
number (not applicable)	45	40		

Statistical analyses

Statistical analysis title	ACR 7 days
Comparison groups	Anti-T Lymphocyte Globulin v Basiliximab
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 1
Method	Chi-squared

Primary: ACR episodes 1 month

End point title	ACR episodes 1 month
End point description: Combination of absence of ACR (Acute Cellular Rejection) episodes and eGFR ≥ 60mL/min/1.73m2	
End point type	Primary
End point timeframe: 1 month after transplantation	

End point values	Anti-T Lymphocyte Globulin	Basiliximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percent				
number (not applicable)	50	55		

Statistical analyses

Statistical analysis title	ACR 1 month
Comparison groups	Anti-T Lymphocyte Globulin v Basiliximab
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 1
Method	Chi-squared

Secondary: Renal function 1 month

End point title	Renal function 1 month
End point description: Recovery of renal function as eGFR ≥60 mL/min/1.73m2	
End point type	Secondary
End point timeframe: 1 month after transplantation	

End point values	Anti-T Lymphocyte Globulin	Basiliximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percent				
number (not applicable)	50	55		

Statistical analyses

Statistical analysis title	Renal function recovery
Comparison groups	Anti-T Lymphocyte Globulin v Basiliximab
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.05
Method	Chi-squared

Secondary: Renal function 1 year

End point title	Renal function 1 year
End point description:	
End point type	Secondary
End point timeframe:	
1 year after transplantation	

End point values	Anti-T Lymphocyte Globulin	Basiliximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: ml/min/1.73m2				
arithmetic mean (standard deviation)	58 (± 16)	62 (± 16)		

Statistical analyses

Statistical analysis title	Renal function 1 year
Comparison groups	Anti-T Lymphocyte Globulin v Basiliximab
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.31
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
One year	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12
Reporting groups	
Reporting group title	ATG group
Reporting group description: -	
Reporting group title	BAS group
Reporting group description: -	

Serious adverse events	ATG group	BAS group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	ATG group	BAS group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	7 / 20 (35.00%)	
Immune system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Thrombocytopenia and Leukopenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal			

disorders			
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Infections and infestations			
Cholangitis			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
MRSA	Additional description: Methicillin-resistant Staphylococcus aureus infection		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

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.

Low number of patients owing to the exploratory nature of the trial and bias in inclusion criteria. Patients with severe thrombocytopenia or leucopenia were not included in the ATG group. Prospective studies are required to confirm these results

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30186817