Clinical trial results:
The BRIDGE-PMR study: B-cell depletion with Rituximab for Dose reduction of Glucocorticoids: Efficacy in PolyMyalgia Rheumatica

Summary

EudraCT number	2018-002641-11
Trial protocol	NL
Global end of trial date	19 August 2020

Results information

Result version number	v1 (current)
This version publication date	02 December 2021
First version publication date	02 December 2021
Summary attachment (see zip file)	BRIDGE-PMR article (BRIDGE-PMR artikel Lancet Rheumatology def.pdf)

Trial information

Trial identification

Sponsor protocol code	BRIDGE-PMR

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sint Maartenskliniek
Sponsor organisation address	Hengstdal 3, Nijmegen, Netherlands, 6500 GM
Public contact	Principal investigator, Sint Maartenskliniek, +31 0243659985, a.vandermaas@maartenskliniek.nl
Scientific contact	Principal investigator, Sint Maartenskliniek, +31 0243659985, a.vandermaas@maartenskliniek.nl

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	14 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2020
Global end of trial reached?	Yes
Global end of trial date	19 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of rituximab, and explore whether it has a glucocorticoid-sparing effect, in recently diagnosed and relapsing patients with polymyalgia rheumatic

Protection of trial subjects:

Monitoring and quality assurance was established following the advice of the NFU. Research conduct was according to WMO, WBP, WGBO, 'richtlijn kwaliteitsborging mensgebonden onderzoek', 'code goed gedrag', and 'code goed gebruik'. The classification for risk was estimated negligible risk since there is a small chance of frequent and or serious adverse events. Therefore the monitoring consisted of the following:
- Frequency of one visit per year
- Check of rate of inclusion and dropout
- Investigator file: presence and completeness
- Check for written informed consent in 10% of participants
- Check for in- and exclusion criteria of the first 3 participants and 10% of the following participants
- Verification of source data of 10% of the participants
- Check for missed SAE's in 10% of the participants and verify reported SAE's
- Check if the laboratory and the department of radiology are certified
- Monitoring was executed by a qualified monitor of the department of Research of the Sint Maartenskliniek Nijmegen, who has successfully attended the BROK-course or equivalent GCPII training.
- Monitoring frequency: at initiation and afterwards yearly of 5 patients per time
Although not formally obligated, a data safety monitoring board (DSMB) of independent professionals was installed to monitor study conduct, recruitment, AE reporting. The DSMB met every 3 months.

Background therapy:

All patients received the same prednisolone treatment. A regular glucocorticoid tapering scheme was started with 15mg per day and than slowly tapered accorinding to local usual care protocol, which was accelerated after 11 weeks to stop at week 18. When a patient experienced a relapse after initial response (secondary non-responder), prednisolone was increased up to the last effective dose for 2 weeks and the accelerated tapering scheme was resumed when remission was reported again. If a second relapse occurred, the prednisolone dose was again increased to the last effective dose and after 2 weeks was subsequently tapered according to the slower, local usual care tapering scheme. In case of recurrence of disease after glucocorticoid cessation, prednisolone was reinitiated and subsequently tapered (accelerated approach or usual care depending on if it was the first or second relapse during the study). All patients received osteoporosis prophylaxis (alendronic acid 70 mg per week and calcium carbonate 500 mg plus colecalciferol 800 units). Use of non-steroidal anti-inflammatory drugs (NSAIDs) was permitted when
necessary.

Evidence for comparator:

Glucocorticoids remain the cornerstone of polymyalgia rheumatica treatment, but their use has several drawbacks, such as long treatment duration and glucocorticoid-related adverse events. Effective glucocorticoidsparing agents with a strong evidence base in polymyalgia rheumatica are absent. As polymyalgia rheumatica is not clearly associated with autoantibodies, it does not appear to be a typical B-celldriven disease. However, B cells are part of the inflammatory cascade and produce interleukin (IL)-6, which is
involved in the pathogenesis of polymyalgia rheumatica. In addition, disturbed B-cell homeostasis was reported in patients with newly diagnosed, untreated polymyalgia rheumatica and giant cell arteritis (a large-vessel vasculitis associated with polymyalgia
rheumatica), and there has been one case report of a patient with giant cell arteritis with polymyalgia rheumatica who was successfully treated with rituximab. Therefore, although not yet supported by

strong evidence, B cells might have a pathophysiological role in polymyalgia rheumatica. Rituximab is a chimeric monoclonal antibody against CD20. There is sufficient clinical experience in other inflammatory rheumatic diseases to show that rituximab is well tolerated. Advantages of this drug include that it is safe, although rituximab can cause infusion-related side-effects and there is a dose-dependent risk of infection.

Actual start date of recruitment	03 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	26
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between Jan 14, 2019, and March 10, 2020, 116 patients were screened and 49 (42%) were enrolled and randomly assigned. Patients from throughout the Netherlands were included.

Pre-assignment

Screening details:

Inclusion: 2012 EULAR/ ACR polymyalgia rheumatica classification, recently diagnosed and relapsers on prednisolone>7.5 mg. Glucocorticoid use over 30mg/ day, use of immunesuppressant drugs in the last 4 months, other rheumatic inflammatory diseases were important exclusion criteria.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

An independent pharmacist generated the randomisation scheme by computerised procedure with varying block size (2 blocks of 20 participants, 1 block of 10). Treatment allocation was not revealed to patients until at least 1 year after infusion. Researchers were unmasked only after analyses of the primary efficacy outcome were completed. Rituximab and placebo were prepared by the local hospital pharmacy. It was impossible to discern between the two

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

A single infusion of 1000 mg rituximab with premedication (single dose intravenous methylprednisolone 50 mg, oral paracetamol 1000 mg, and oral cetirizine 10 mg)

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

A single infusion of Rituximab (Rixathon, Sandoz, Holzkirchen, Germany; ATC code L01X C02) 500 mg concentrate for solution for infusion was given. Each 50 mL vial contains 500 mg of rituximab and was diluted in 500 mL in sodium chloride 0.9%. Premedication was given: single dose intravenous methylprednisolone 50 mg, oral paracetamol 1000 mg, and oral cetirizine 10 mg

Arm title	Placebo

Arm description:

A single intravenous infusion of placebo consisting of sodium chloride 0,9%, indiscernable from the rituximab infusion

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Placebo

Number of subjects in period 1	Rituximab	Placebo
Started	24	25
Completed	24	25

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
A single infusion of 1000 mg rituximab with premedication (single dose intravenous methylprednisolone 50 mg, oral paracetamol 1000 mg, and oral cetirizine 10 mg)	
Reporting group title	Placebo
Reporting group description:	
A single intravenous infusion of placebo consisting of sodium chloride 0,9%, indiscernable from the rituximab infusion	

Reporting group values	Rituximab	Placebo	Total
Number of subjects	24	25	49
Age categorical			
Participants werd over 50 years old.			
Units: Subjects			
Adults (18-64 years)	15	11	26
From 65-84 years	9	14	23
85 years and over	0	0	0
Age continuous			
rituximab group: mean (SD) age 64 (8) placebo group: mean (SD) age 66 (10)			
Units: years			
arithmetic mean	64	66	
standard deviation	± 8	± 10	-
Gender categorical			
Units: Subjects			
Female	12	13	25
Male	12	12	24

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description:	
A single infusion of 1000 mg rituximab with premedication (single dose intravenous methylprednisolone 50 mg, oral paracetamol 1000 mg, and oral cetirizine 10 mg)	
Reporting group title	Placebo
Reporting group description:	
A single intravenous infusion of placebo consisting of sodium chloride 0,9%, indiscernable from the rituximab infusion	

Primary: Glucocorticoid free remission

End point title	Glucocorticoid free remission
End point description:	
Percentage of patients with glucocorticoid free remission at week 21 after RTX/PBO infusion , where remission was defined as PMR-activity score<10.	
End point type	Primary
End point timeframe:	
21 weeks	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: percentage				
GC free remission	11	5		

Statistical analyses

Statistical analysis title	low dose glucocorticoid (5mg or less per day)
Statistical analysis description:	
patients that achieved low dose glucocorticoid at week 21	
Comparison groups	Placebo v Rituximab
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	46

Confidence interval	
level	95 %
sides	1-sided
lower limit	20
Variability estimate	Standard deviation

Notes:

[1] - one sided
n=23 (100% in the rituximab group versus n=13 (54%) in the placebo group

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
During 21 weeks	
Adverse event reporting additional description:	
Safety endpoints were any glucocorticoid-related and rituximab-related adverse events, graded according to Common Terminology Criteria for Adverse Events version 5.0. An elaborate assessment of glucocorticoidrelated toxicity was assessed at baseline, 11 and 21 weeks using the glucocorticoid toxicity index	
Assessment type	Systematic

Dictionary used	
Dictionary name	common terminology
Dictionary version	5

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please see the reference to the article for full publication of all adverse events

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2019	the cutoff point of remission by the polymyalgia rheumatica activity score, the classification criteria used for study inclusion, the inclusion of not only glucocorticoidnaive patients but also patients on short-term glucocorticoid treatment, and the inclusion of relapsing patient

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 March 2020	due to COVID pandemic trial was ended prematurley, falling three inclusions short of the intended 50	-

Notes:

Limitations and caveats

None reported