



## Clinical trial results: mycophenylate mofetil and tacrolimus vs tacrolimus alone for the treatment of nephrotic syndrome secondary to idiopathic membranous glomerulonephritis

### Summary

EudraCT number	2008-001009-41
Trial protocol	GB
Global end of trial date	19 September 2018

### Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

### Trial information

#### Trial identification

Sponsor protocol code	grim1001
-----------------------	----------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00843856
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	ImperialCollegeNHSTrust
Sponsor organisation address	Du Cane Road, London, United Kingdom,
Public contact	Megan Griffith, Imperial College NHS Trust, +44 0208383527, <a href="mailto:megan.griffith1@nhs.net">megan.griffith1@nhs.net</a>
Scientific contact	Megan Griffith, ImperialCollegeNHSTrust, +44 0208383527, <a href="mailto:megan.griffith1@nhs.net">megan.griffith1@nhs.net</a>

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 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 September 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate if the addition of mycophenylate mofetil to standard therapy with tacrolimus prevents relapse of nephrotic syndrome in patients with idiopathic membranous glomerulonephritis

Protection of trial subjects:

All patients were regularly seen and monitored in the renal clinic at Hammersmith Hospital London.

Background therapy:

All patients were given supportive therapy which included ace inhibitors angiotensin receptor blockers diuretics, statins and anticoagulation as clinically indicated.

Evidence for comparator:

Calcineurin inhibitors (CNIs) such as cyclosporin and tacrolimus (TAC) are commonly used for the treatment of Membranous Glomerulonephritis (MGN) and are effective in inducing remission. Their antiproteinuric effect has been clearly documented; however relapses after discontinuation are common and there is a concern about nephrotoxicity after prolonged use. Although their main mode of action is immunomodulatory they also have a significant antiproteinuric effect which is attributed to their haemodynamic effect on glomerular perfusion as well as to their direct effect on podocytes. A study comparing tacrolimus to placebo showed that TAC alone is effective in achieving remission but patients often relapse after treatment withdrawal. A recent trial comparing rituximab to cyclosporine also showed a high relapse rate of the cyclosporine arm after treatment withdrawal. Mycophenolate mofetil (MMF) has been used for the treatment of MGN in regimens of variable dosing and duration, either alone or in combination with steroids. MMF monotherapy is not effective in inducing remission; however it has been successfully used in combination with steroids. MMF has a long history of use in combination with CNIs in transplantation with a good safety profile and this combination has also been used in nephrotic syndrome secondary to other glomerulonephritides such as lupus nephritis. The presence of anti-PLA2R auto-antibodies in a significant number of patients with MGN suggests that an immunosuppressive agent such as MMF, that suppresses B lymphocyte proliferation and antibody formation, may be particularly effective in inducing and maintaining immunological and clinical remission in MGN. We therefore compared the efficacy of combination treatment with tacrolimus and mycophenolate mofetil versus tacrolimus alone for achieving sustained remission in patients with Idiopathic Membranous Glomerulonephritis.

Actual start date of recruitment	03 March 2009
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	United Kingdom: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

<b>Subjects enrolled per age group</b>	
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)	34
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from the glomerulonephritis clinic at Hammersmith Hospital, London from march 2009 to December 2014.

### Pre-assignment

Screening details:

Patients with Membranous Glomerulonephritis, diagnosed on renal biopsy, with nephrotic syndrome after 3 months of ace inhibitors or angiotensin receptor blockers.

### Period 1

Period 1 title	tacrolimus vs mycophenylate mofetil (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	tacrolimus

Arm description:

2mg twice daily tacrolimus titrated to archive whole blood levels of 5-12ng/ml

Arm type	Active comparator
Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2mg twice daily

<b>Arm title</b>	tacrolimus and mycophenylate mofetil
------------------	--------------------------------------

Arm description:

tacrolimus and mycophenylate mofetil

Arm type	Experimental
Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	prograff
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2mg twice a day titrated to achieve blood levels of 5-12ng/L

Investigational medicinal product name	mycophenylate mofetil
Investigational medicinal product code	
Other name	cellcept
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg twice a day titrated to achieve blood mycophenylate acid levels of 1.5-3 mg/L

Number of subjects in period 1	tacrolimus	tacrolimus and mycophenylate mofetil
Started	20	20
Completed	19	18
Not completed	1	2
Lost to follow-up	1	2

## Baseline characteristics

### Reporting groups

Reporting group title	tacrolimus
Reporting group description: 2mg twice daily tacrolimus titrated to archive whole blood levels of 5-12ng/ml	
Reporting group title	tacrolimus and mycophenylate mofetil
Reporting group description: tacrolimus and mycophenylate mofetil	

Reporting group values	tacrolimus	tacrolimus and mycophenylate mofetil	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	15	34
From 65-84 years	1	5	6
85 years and over	0	0	0
Age continuous Units: years			
median	55	48	
full range (min-max)	24 to 68	28 to 66	-
Gender categorical Units: Subjects			
Female	9	7	16
Male	11	13	24
Serum albumin Units: g/L			
median	17	18	
full range (min-max)	8 to 30	11 to 27	-
Estimated glomerus filtration rate (GRF) Units: mls/min/1.73m2			
median	109	121	
full range (min-max)	44 to 142	63 to 201	-

## End points

### End points reporting groups

Reporting group title	tacrolimus
Reporting group description:	
2mg twice daily tacrolimus titrated to archive whole blood levels of 5-12ng/ml	
Reporting group title	tacrolimus and mycophenylate mofetil
Reporting group description:	
tacrolimus and mycophenylate mofetil	

### Primary: number of patients who gained remission from the nephrotic syndrome who subsequently relapsed

End point title	number of patients who gained remission from the nephrotic syndrome who subsequently relapsed
End point description:	
In the TAC group 16/20 achieved remission compared to 19/20 (95%) in the TAC/MMF group (p=0.34). There was no difference between the groups in the number of patients who subsequently relapsed. In the TAC group 8/16 patient(50%) relapsed and in the TAC/MMF group 8/19 patients (42%) relapsed (p=0.7).	
End point type	Primary
End point timeframe:	
Initially measured at 6 months after stopping treatment and monitored until the end of the trial.	

End point values	tacrolimus	tacrolimus and mycophenylate mofetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16 <sup>[1]</sup>	19 <sup>[2]</sup>		
Units: patients	8	8		

Notes:

[1] - number of patients who achieved remission

[2] - number of patients who achieved remission

### Statistical analyses

Statistical analysis title	Relapsed
Comparison groups	tacrolimus v tacrolimus and mycophenylate mofetil
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7
Method	Fisher exact

### Secondary: Number of patient achieved remission

End point title	Number of patient achieved remission
-----------------	--------------------------------------

---

End point description:

---

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

---

End point timeframe:

1 year

---

End point values	tacrolimus	tacrolimus and mycophenylate mofetil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: patient	16	19		

### Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Reported throughout the trial, 10 years

Adverse event reporting additional description:

Review of patients in OP and reporting of all admissions

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

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	10
--------------------	----

### Reporting groups

Reporting group title	tacrolimus
-----------------------	------------

Reporting group description: -

Reporting group title	tacrolimus and mycophenolate mofetil
-----------------------	--------------------------------------

Reporting group description: -

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: None serious adverse event occurred.

Serious adverse events	tacrolimus	tacrolimus and mycophenolate mofetil	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)	3 / 20 (15.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidectomy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	3 / 20 (15.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute kidney injury			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestatic jaundice			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	tacrolimus	tacrolimus and mycophenolate mofetil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	

## 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

None reported

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31492152>