



MSC AFTER DECEASED DONOR LIVER TRANSPLANTATION: A PHASE I/II STUDY OF THE UNIVERSITY OF LIEGE

Dr O Detry MD PhD

Dpt of Abdominal Surgery & Transplantation
CHU Liège, University of Liège, Belgium
olivier.detry@transplantation.be



INFUSION OF THIRD-PARTY MESENCHYMAL STROMAL CELLS (MSC) AFTER KIDNEY OR LIVER TRANSPLANTATION: A PHASE I-II, OPEN-LABEL, CLINICAL STUDY

(EudraCT 2011-001822-81 & NCT01429038)

O Detry, M Vandermeulen, MH Delbouille, J Somja, N Bletard, A Briquet,
C Lechanteur, O Giet, E Baudoux, M Hannon, F Baron, Y Beguin

Dpts of Abdominal Surgery & Transplantation, Pathology, and Hematology
Laboratory of Cell and Gene Therapy (LTCG)

CHU Liège, GIGA-R, University of Liège, Belgium

Background

- MSC may have an immunosuppressive and/or immunoregulatory effect
 - MSC are clinically used in GVHD after BM Tx
- MSC may have an anti-inflammatory effect
- MSC may have an effect in organ regeneration
- MSC may protect from I/R injury

- Role of MSC in SOT?

Background: MSC in SOT ?

- Pulmonary embolism ?
- Cytokine-release syndrome ?
- Allergy ?
- Anti-HLA immunisation ?
- Over immunosuppression ?
- Cancer ?
- Graft vascular thrombosis ?

Objectives

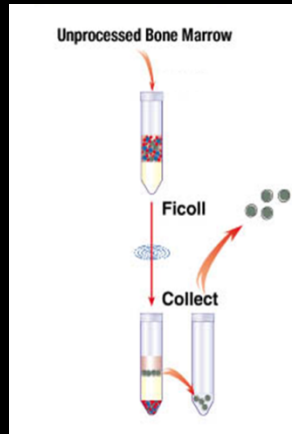
- Primary endpoint: feasibility & safety for LT recipients
 - tolerability of infusion
 - infections (bacterial, viral, fungi)
 - cancers (PTLD, others)
 - patient and graft survivals
- Secondary endpoint 1: immunosuppression
 - rejection rate
 - biopsy
 - blood immune profile
- Secondary endpoint 2: graft function & biopsy

MSC

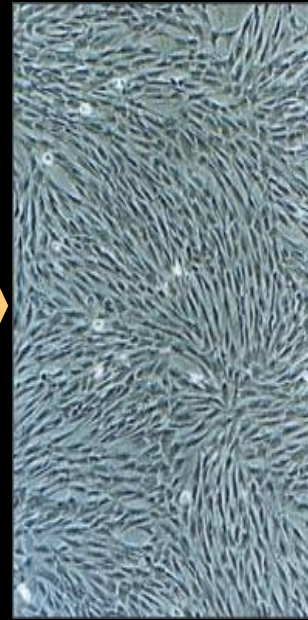
Cell production



**Bone marrow
collection
(volunteer)**



**MNC
isolation**



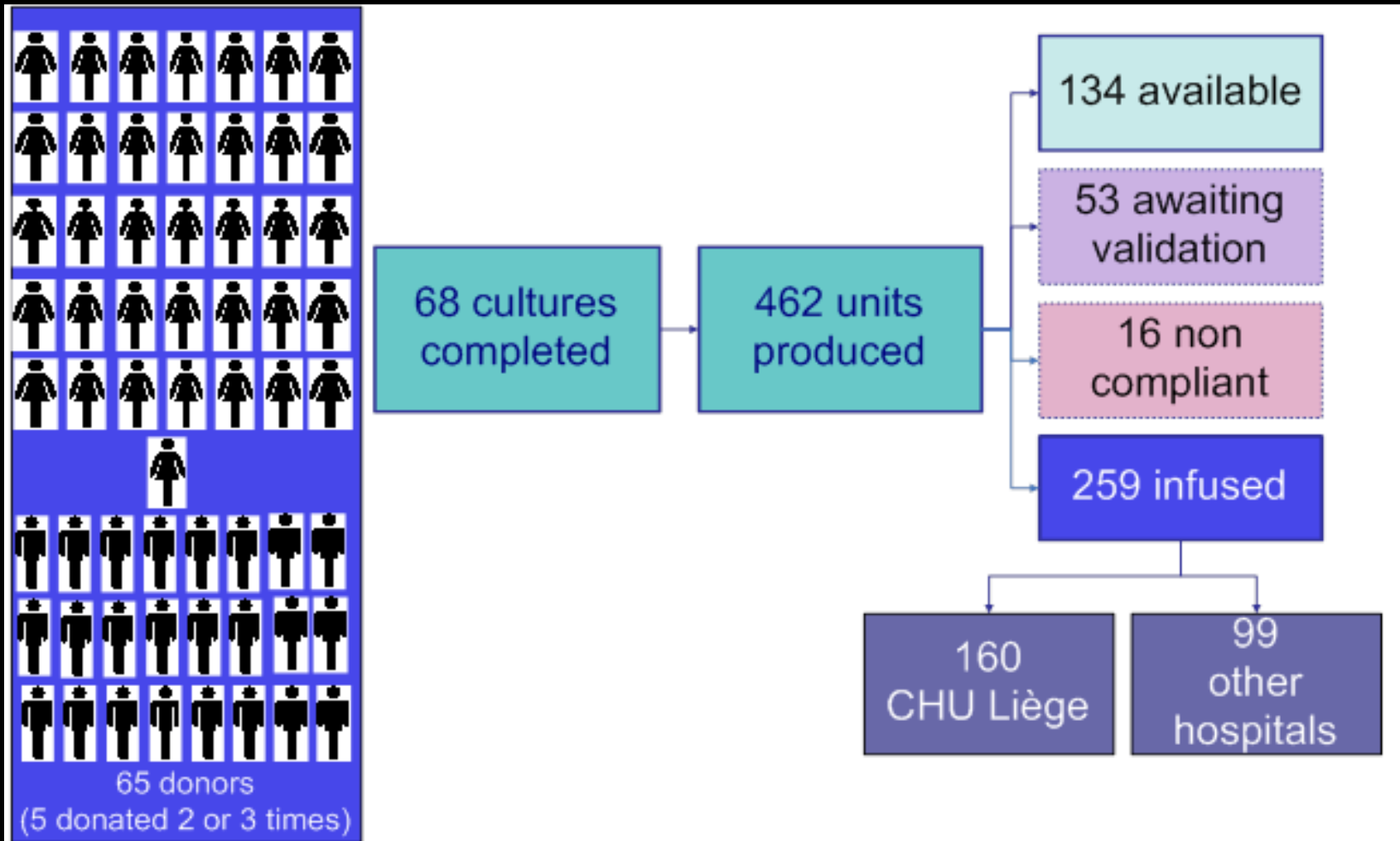
**Culture
(4 weeks)
Expansion**



**Freezing
& banking**

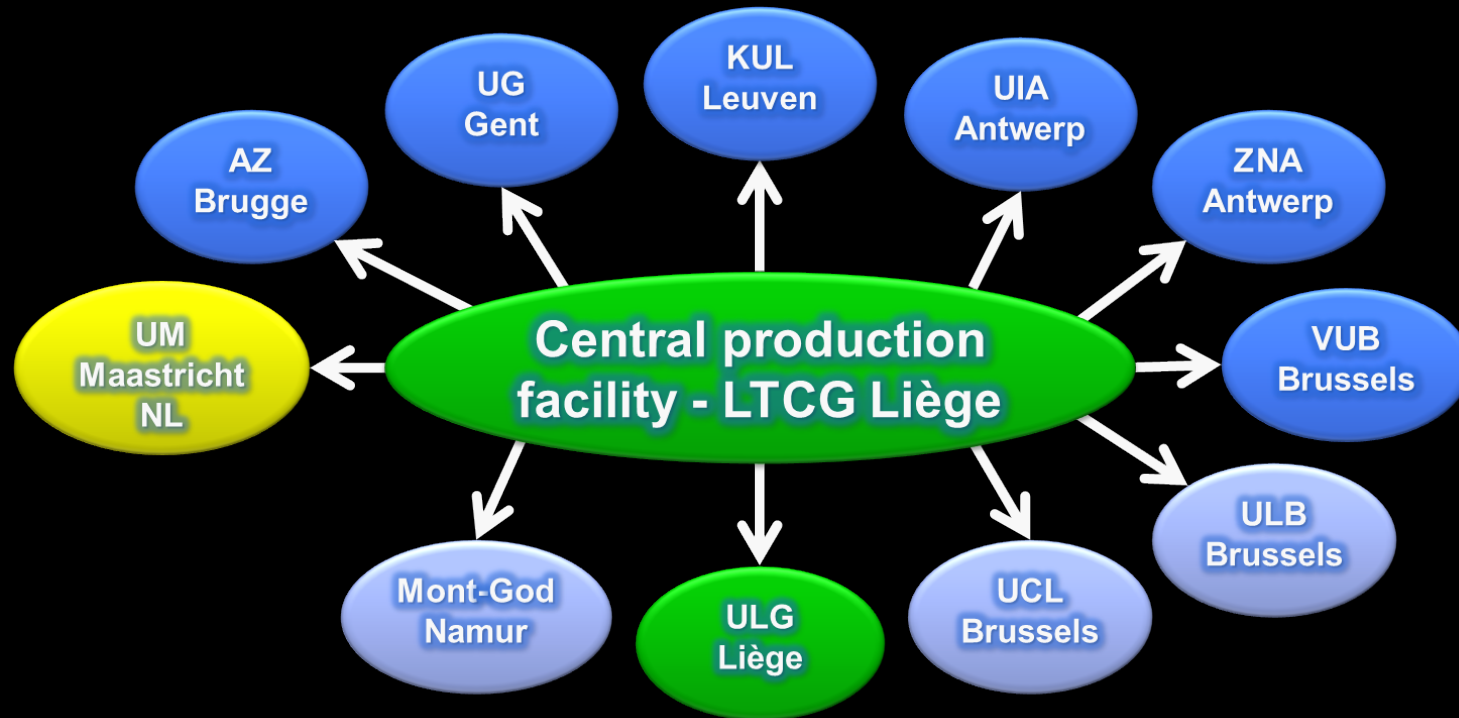
MSC

MSC bank

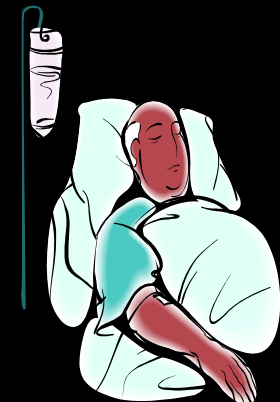


ALLOGENEIC MSC

BHS transplant clinical network



6 clinical trials



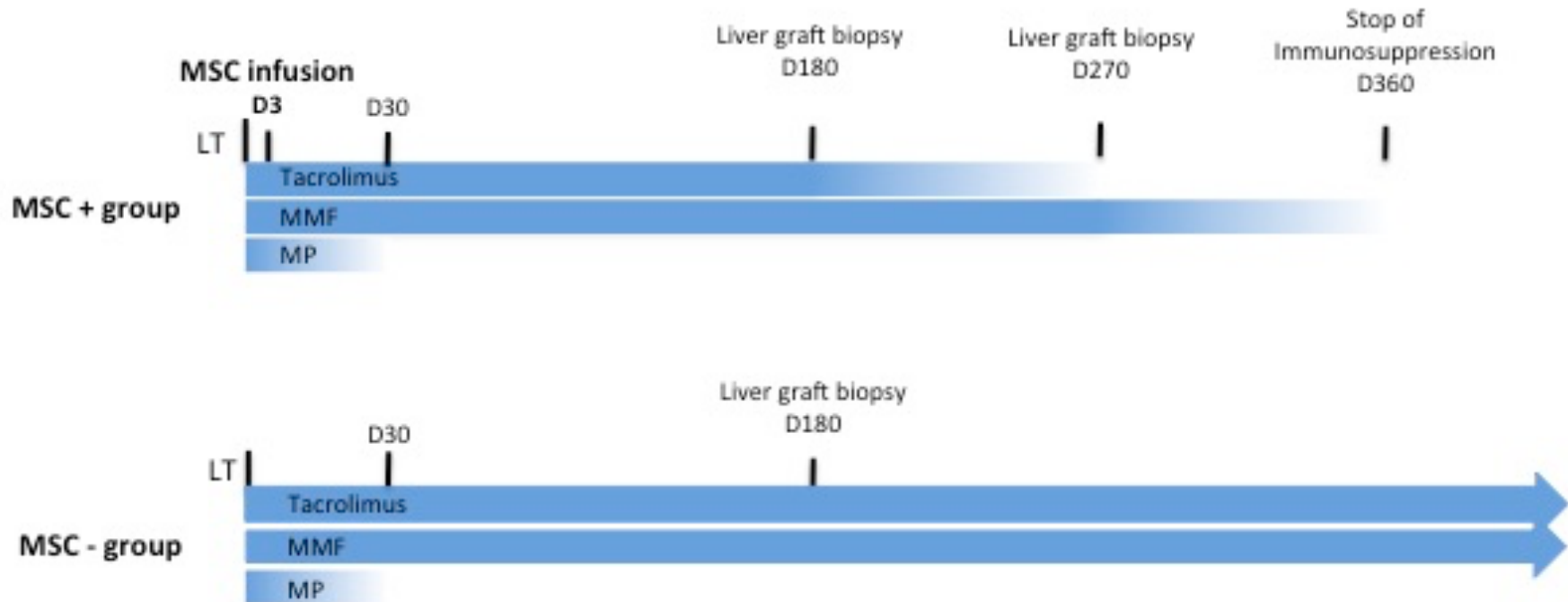
M&M

- Cadaveric liver recipients (DBD & DCD)
- Classical immunosuppressive management
- Dose: 1.5 to 3 . 10^6 MSC/kg
- Central IV injection at day 3 +/-2 post Tx

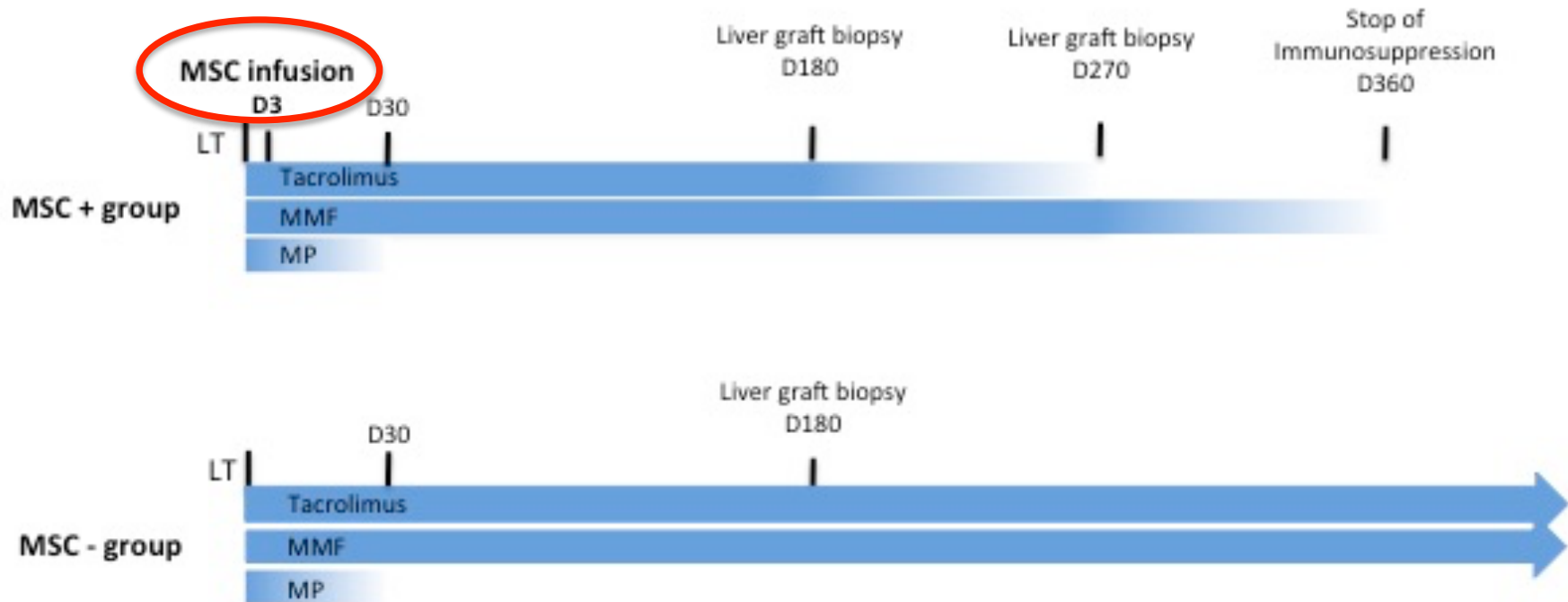
M&M: liver 1

- Liver transplantation
 - 2 groups: -10 MSC +: MSC group
 - 10 MSC -: Control group
 - prospective, no randomisation, unblinded
 - regular immunosuppression (TAC-MMF)
 - protocol biopsy at month 6 in both groups
 - follow-up of one year completed for all patients
- MSC group:
 - tapering of TAC from month 6 to 9, then biopsy
 - tapering MMF from month 9 to 12

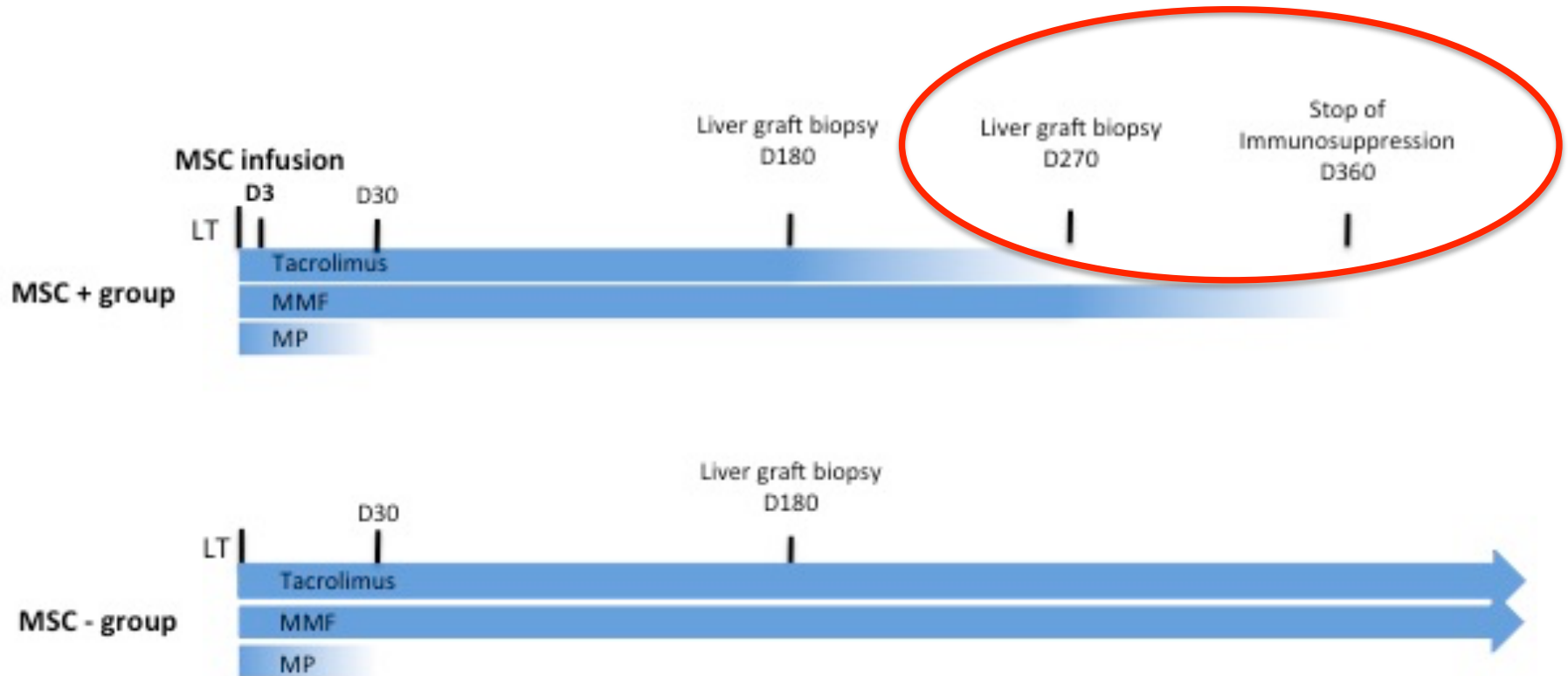
M&M



M&M



M&M



M&M

- Blood: FACS, Tregs, Ig, anti-HLA
- Biopsies:
 - Histology
 - Immunohistology banking of serum & biopsies

March 2012



Liver recipients

		MSC+ (n=10)	MSC- (n=10)	<i>P</i>
Age (years)		62.5 (47-74)	58 (52-69)	0.516
Male/Female		8/2	7/3	1
Lab MELD		16.5 (6-29)	15 (8-38)	0.491
BMI		25.7 (20.9-38.2)	25.6 (22.2-33.0)	0.541
Liver disease				
	Post alcoholic cirrhosis	5	5	
	NASH	3	0	
	HCC	2	5	

Median (Ranges) or *n* (Mann Whitney or Fischer test)

Liver donors & Transplantations

	MSC+ group (n=10)	Control group (n=10)	<i>P</i>
Age (years)	57 (17-77)	54 (18-79)	0.985
Male/Female	4/6	6/4	0.656
CPR (Y/N)	4/6	3/7	1
Donor type (DBD/DCD)	4/6	5/5	1
BMI (kg/m²)	24 (21-31)	25 (22-29)	0.510
Intensive care stay (days)	4 (1-75)	6.5 (2-29)	0.401
Urinary output (mL/h)	82 (7-160)	127.5 (47-357)	0.096
Pressors (Y/N)	5/5	6/4	1
Na (mmol/L)	144 (133-155)	144.5 (141-160)	0.445
Total bilirubin (mg/dL)	0.35 (0.30-1.59)	0.32 (0.15-0.85)	0.668
AST (U/L)	38 (23-190)	48.5 (26-91)	0.615
GGT (U/L)	59.5 (14-256)	68 (12-144)	0.888
CIT (min)	229 (149-800)	345 (181-713)	0.386
TIT (min)	317.5 (186-831)	402.5 (216-754)	0.519

Median (Ranges) or *n* (Mann Whitney or Fischer test)

MSC injection in LT recipients

	Per protocol	Study (Median) (IQR; Ranges)
MSC Injection day	day 3 +/- 2	3 (3-3.25; 2-5)
Dose MSC (10 ⁶ /kg)	1.5-3	2.1 (2.0-2.4; 1.9-2.7)
Injection volume (ml)		342 (322-469; 306-614)
Injection duration (min)		25 (16.2-40; 11-60)

Median (IQR; Ranges)

Infusional toxicity

	Pre Infusion	15 min	End of infusion	<i>P</i>
Body temperature (°C)	36.0 (35.4-37.7)	36.3 (35-36.9)	36.2 (35.5-37)	0.87
Mean PA (mmHg)	103.3 (87-124)	107 (84-119.5)	106 (94-115)	0.83
Heart rate (per min)	81 (65-102)	82.5 (65-102)	80.5 (68-101)	0.17
NI O2 saturation	99 (93-100)	100 (92-100)	97.5 (93-100)	0.67

Median (Ranges) (Friedman test & ANOVA)

- No hepatic artery or portal vein thrombosis
- No sign of pulmonary embolism or post infusional intubation
- No anaphylactic reaction, no skin reaction

Infectious complications

		MSC group (n=10)	Control group (n = 9)	P
Overall		2	6	0.06
Fungal		0	0	
Viral	CMV disease	0	0	
	HSV	2	0	
	VZV	0	1	
Bacterial	Wound	0	1	
	Urinary	0	2	
	Sinusitis	0	1	
	Pulmonary	0	1	

n (Chi square)

Infectious complications

		MSC group (n=10)	Control group (n = 9)	P
Overall		2	6	0.06
Fungal		0	0	
Viral	CMV disease	0	0	
	HSV	2	0	
	VZV	0	1	
Bacterial	Wound	0	1	
	Urinary	0	2	
	Sinusitis	0	1	
	Pulmonary	0	1	

n (Chi square)

Cancer (6-month follow-up)

	MSC group (n=10)	Control group (n = 9)	P
Overall	1	0	>0.99
de novo	0	0	
HCC recurrence	1	0	

n (Chi square)

Follow-up at 6 months

- No rejection in either groups
- One death in the control group (hepatic artery fistula)

Month-6 graft biopsies

	MSC group (n=10)	Control group (n = 9)	P
Banff	3 (0-6)	4 (0-7)	0.21
Fibrosis	1 (0-2)	1 (0-3)	0.48

median (Ranges)

Blood tests Day 7

	MSC group (n=10)	Control group (n = 9)	P
total bilirubin (mg/L)	10.2 (4.6-26.8)	8.3 (3.7-20.7)	0.21
AST (U/L)	28.5 (19-101)	46 (30-105)	0.16
Alcaline Ph (U/L)	140 (43-475)	256 (172-590)	0.04
GGT (U/L)	218 (29-626)	368 (172-760)	0.24
INR	1.14 (1-1.21)	1.06 (1-1.26)	0.16
creatinine (mg/L)	11.55 (5.7-36)	8.9 (5.9 – 16.9)	0.32
CRP (mg/L)	32.8 (8.4-50.1)	24.6 (12.8-144.3)	0.82
tacrolimus (µg/L)	7.1 (3.1-9)	9 (2.1-11.7)	0.12

median (Ranges)

Blood tests Month 1

	MSC group (n=10)	Control group (n = 9)	P
total bilirubin (mg/L)	5.6 (3.4-11.6)	4.6 (1.3-7.5)	0.34
AST (U/L)	18 (11-51)	16 (9-61)	0.48
Alcaline Ph (U/L)	137.5 (53-554)	144 (103-857)	0.43
GGT (U/L)	101 (26-596)	112 (42-690)	0.82
INR	1.15 (0.97-1.26)	1.08 (1-1.19)	0.53
creatinine (mg/L)	16.2 (5.3-24.4)	14.1 (8.2-27.6)	0.45
CRP (mg/L)	12.9 (4.8-62.2)	17.2 (3.5-73)	0.94
tacrolimus (µg/L)	8.1 (2.4-10)	8 (5-16.3)	0.51

median (Ranges)

Blood tests Month 3

	MSC group (n=10)	Control group (n = 9)	P
total bilirubin (mg/L)	4.8 (3-19.8)	4.3 (2.3-7.5)	0.34
AST (U/L)	20 (14-31)	20 (11-58)	0.79
Alcaline Ph (U/L)	101.5 (56-1461)	119 (86-570)	0.54
GGT (U/L)	58.5 (15-695)	49 (14-332)	0.76
INR	1.1 (0.95-1.29)	1.13 (1.01-1.56)	0.65
creatinine (mg/L)	12.05 (5-25.7)	13.4 (7-21.7)	0.92
CRP (mg/L)	3.1 (1-27.6)	6.8 (1.3-23.5)	0.20
tacrolimus (µg/L)	7.7 (3.7-13)	6.4 (5.2-13.2)	0.61

median (Ranges)

Blood tests Month 6

	MSC group (n=10)	Control group (n = 9)	P
total bilirubin (mg/L)	6.6 (3.7-25.7)	4.6 (0.43-27)	0.27
AST (U/L)	25 (15-44)	24 (14-136)	0.64
Alcaline Ph (U/L)	143.5 (67-1,166)	186 (82-554)	0.26
GGT (U/L)	81 (22-978)	53 (12-2,064)	0.43
INR	1.1 (1-1.26)	1.07 (1-1.17)	0.23
creatinine (mg/L)	11.6 (7.1-18.9)	10.1 (1.28-15.8)	0.30
CRP (mg/L)	3.5 (0.7-36.5)	5.6 (0.9-151)	0.23
tacrolimus (µg/L)	4.9 (2.3-9.3)	7.4 (4.9-13)	0.02

median (Ranges)

Month-6 graft biopsies

	MSC group (n=10)	Control group (n = 9)	P
CD3	196 (95-334)	162 (93-590)	0.86
CD4	101 (54-212)	103 (17-496)	> 0.99
CD8	69 (15-196)	85 (12-300)	0.49
CD68	28.5 (12-75)	40 (15-104)	0.58
CD1a	1 (0-3)	1 (0-3)	0.83
CD138	7.5 (4-38)	6 (2-44)	0.50
CD20	27 (3-95)	28 (10-163)	0.66
FoxP3	2 (0-16)	4 (0-33)	0.49

median (Ranges)

Follow-up at 1 year

- Patient and graft survivals at 90% in both groups

Cancer

	MSC group (n=10)	Control group (n = 9)	P
Overall	1	1	>0.99
de novo	0	0	
HCC recurrence	1	1	

Peripheral Blood Lymphocyte count

Month 1	MSC group (n=10)	Control (n=9)	P
White blood cells (/μL)	6,630 (3,280-9,700)	5,190 (4,150-10,030)	0.67
Lymphocytes (/μL)	855 (380-1,690)	940 (300-1,550)	0.92
CD3 (/μL)	687 (288-1,406)	620 (200-1,336)	0.48
CD45RA (/μL)	119 (50-557)	147 (48-234)	0.70
CD45RO (/μL)	373 (179-516)	201 (79 -609)	0.23
CD3+CD4+ (/μL)	535 (230-978)	349 (128-786)	0.30
CD3+CD56+ (/μL)	27 (1-87)	42 (4-154)	0.35
CD3+CD8+ (/μL)	115 (49-418)	142 (57-336)	0.76
CD19 (/μL)	144 (30-286)	99 (38-369)	0.70
CD56 (/μL)	109 (45-365)	188 (58-618)	0.27

Peripheral Blood Lymphocyte count

Month 3	MSC group (n=10)	Control (n=9)	P
White blood cells (/μL)	5,265 (970-8,160)	5,200 (2,470-7,030)	0.39
Lymphocytes (/μL)	875 (420-1,880)	760 (490-1,760)	0.82
CD3 (/μL)	767 (352-1,225)	553 (274-1,419)	0.30
CD45RA (/μL)	123 (51-389)	82 (54-259)	0.58
CD45RO (/μL)	381 (171-680)	179 (135-765)	0.23
CD3+CD4+ (/μL)	516 (292-923)	285 (202-976)	0.27
CD3+CD56+ (/μL)	21 (1-99)	34 (2-197)	0.76
CD3+CD8+ (/μL)	202 (41-496)	228 (56-362)	0.94
CD19 (/μL)	93 (34-354)	100 (21-321)	0.76
CD56 (/μL)	154 (66-331)	119 (59-550)	0.82

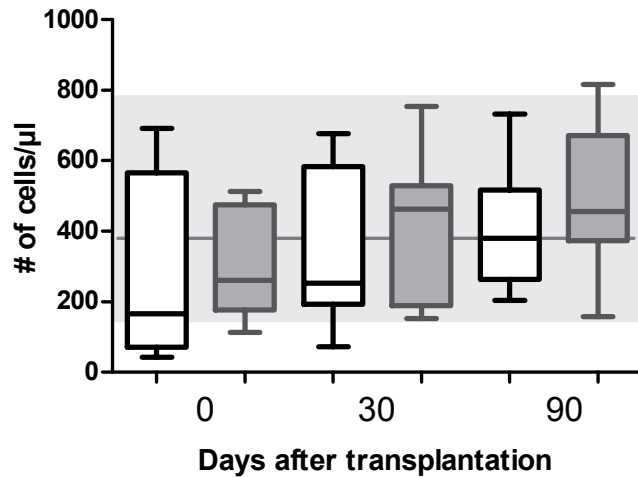
Peripheral Blood Lymphocyte count

Month 6	MSC group (n=10)	Control (n=9)	P
White blood cells (/μL)	4,815 (4,200-8,150)	5,440 (2,680-11,430)	0.99
Lymphocytes (/μL)	1,250 (660-2,260)	1,000 (540-1,340)	0.23
CD3 (/μL)	880 (395-2,098)	592 (342-1,366)	0.27
CD45RA (/μL)	127 (76-364)	108 (61-298)	0.58
CD45RO (/μL)	396 (214-615)	267 (156-864)	0.20
CD3+CD4+ (/μL)	623 (348-728)	359 (224-1,163)	0.20
CD3+CD56+ (/μL)	31 (1-91)	36 (3-117)	0.54
CD3+CD8+ (/μL)	238 (38-1,471)	210 (73-345)	0.70
CD19 (/μL)	99 (25-256)	192 (52-258)	0.27
CD56 (/μL)	191 (66-386)	210 (55-490)	>0.99

Peripheral blood CD4+ T cells

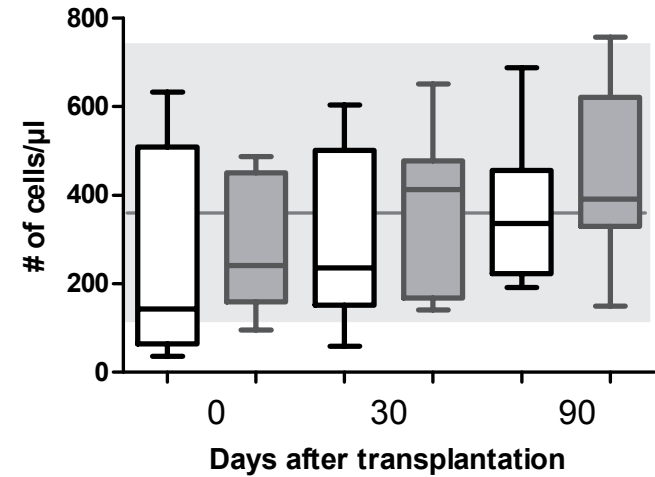
A

CD4 T cells



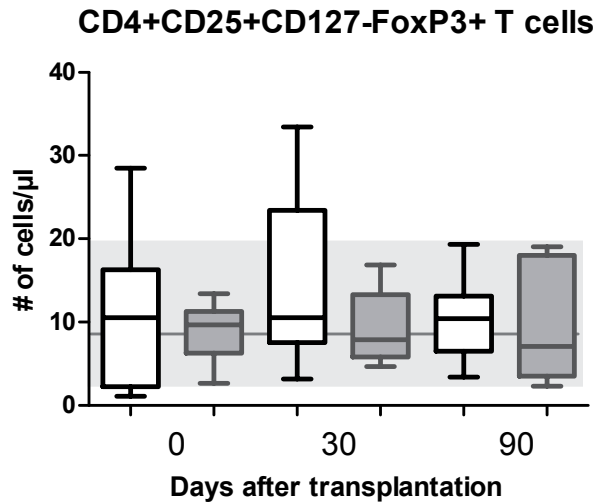
B

Tconv

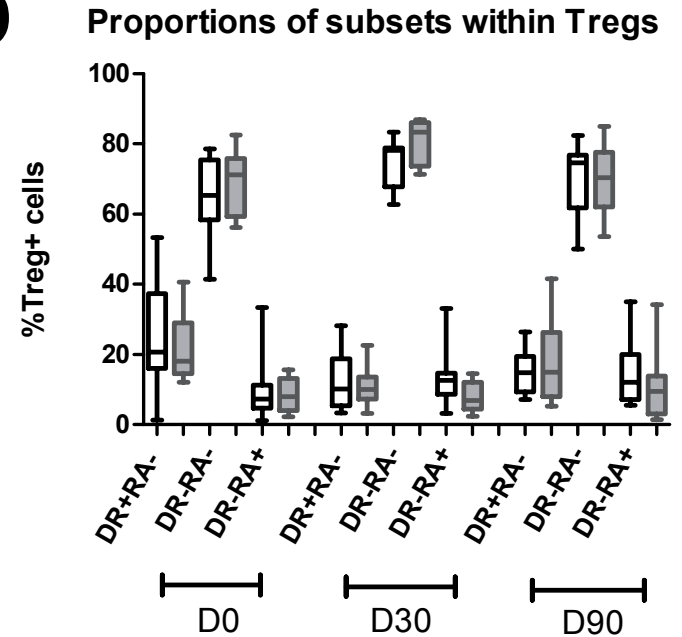


Peripheral blood CD4+ T cells

C



D



HLA

- HLA liver recipient
- HLA liver donor
- HLA MSC donor

- CDC
- Luminex

anti - HLA

- CDC ≠ Luminex
- Control group
 - anti-HLA: liver donor
 - anti-HLA: other – transfusion?

Phase 2 trial: IS weaning

- 9 MSC + patients underwent MSC weaning attempt (first TACRO, then MMF)
- 1 patient was successfully weaned
- 2 patients were on MMF monotherapy at month 9, but did not “tolerate” MMF weaning
- 6 patients had increasing liver tests during TACRO weaning

Conclusions

- Third party MSC infusion is feasible and seems safe in LT recipients
- Weaning of IS after one single injection of MSC in LT patients under TAC-MMF is not possible
- Timing? dose? number? source? IS?

Present & Future

- MSC Lab (Dr François Jouret)
- GMP accreditation of the MSC
- Complete results of the kidney – MSC trial

- Phase 2 trial
- Repeated allo MSC infusion in 10 liver transplants with tolerogenic IS protocol (basilixumab – everolimus – MMF – low dose steroids and progressive IS weaning)

Thanks to:

- **Hematology & LTCCG**
 - Pr Y Beguin, Pr F Baron, Dr E Baudoux, Mrs C Lechanteur
- **Surgery & Transplantation**
 - Pr O Detry, Mrs MH Delbouille, Dr Vandermeulen, Dr N Meurisse, Pr P Honoré
- **Nephrology**
 - Dr L Weekers, Dr C Bonvoisin, Dr F Jouret, Dr P Erpicum
- **Pathology**
 - Pr P Delvenne, Dr J Somja Dr N Bletard
- **GIGA CV sciences**
 - Dr P Erpicum, P Rowart, L Poma, Dr M Vandermeulen, Dr F Jouret

Sponsors

