



2ND SCIENTIFIC SYMPOSIUM OF THE WBMT

Salvador -Bahia, Brazil

Stem Cell Transplantation in Autoimmune Diseases

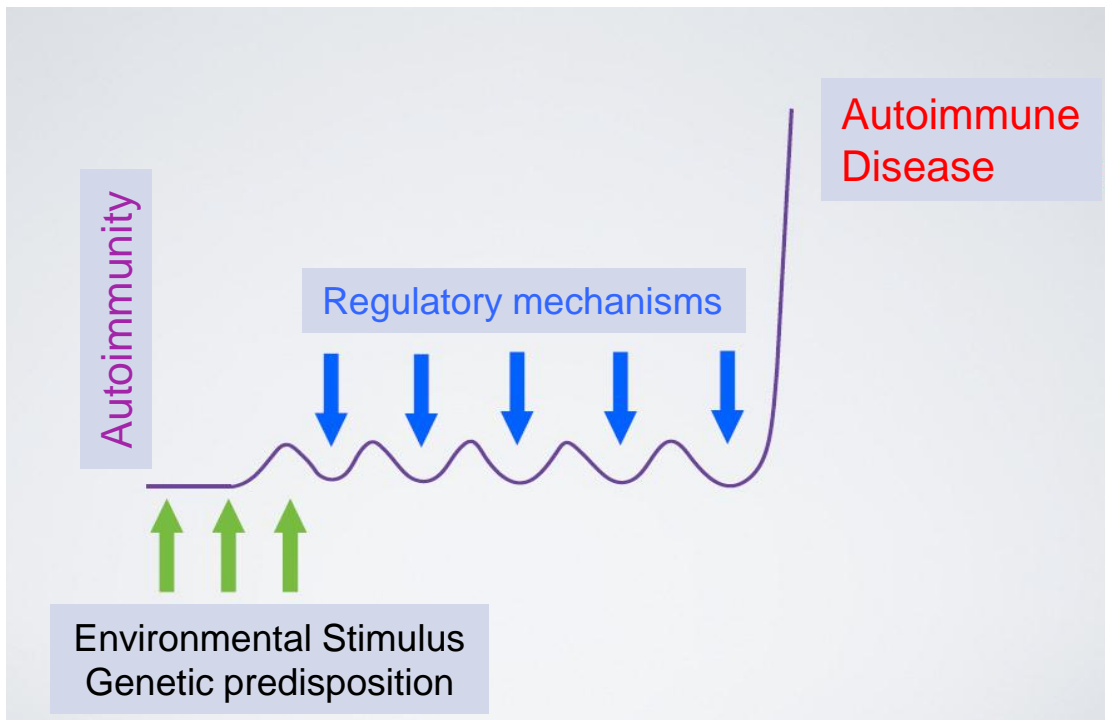
Belinda P. Simões

Medical School Ribeirão Preto - University of São Paulo -Brazil



SCT in autoimmune disease

- ▶ Autoimmune disease
 - ▶ Heterogenous group of more than 100 disorders
 - ▶ Affect about 5 -8% of world's population
 - ▶ Aberrant activation of the immune system





SCT in autoimmune disease

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▶ The evidence

- ▶ Animal models

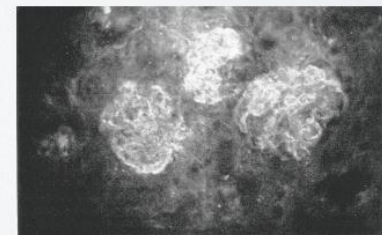
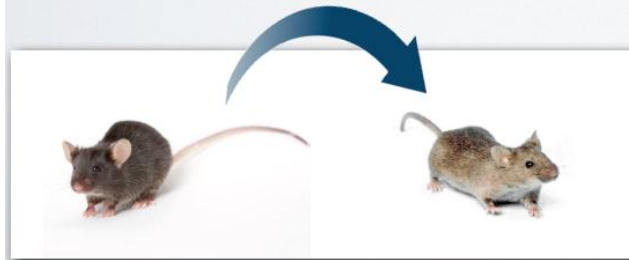
ADOPTIVE TRANSFER OF THE DISEASES OF NEW ZEALAND BLACK MICE TO NORMAL MOUSE STRAINS

A. M. DENMAN, A. S. RUSSELL AND EVELYN J. DENMAN

*M.R.C. Rheumatism Research Unit,
Canadian Red Cross Hospital, Taplow, Maidenhead, Berkshire*

Transferência de autoimunidade

Clin Exp Immunol 1969





SCT in autoimmune disease

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 - ▶ Affect about 5 -8% of world's population
 - ▶ Aberrant activation of the immune system
- ▶ The evidence
 - ▶ Animal models

Coincidental autoimmune disease in patients transplanted for conventional indications

Alberto M. Marmont*

Professor Emeritus

Division of Hematology and Stem Cell Transplantation Centre, S Martino's Hospital, Largo Rosanna Benzì 10, 16132 Genoa, Italy

| <u>DISEASE</u> | <u>n</u> | <u>REMISSIONS</u> |
|------------------------------------|----------|--------------------------|
| <u>Allogeneic transplants</u> | | |
| Rheumatoid arthritis (RA) | 10 | 04 complete/06 temporary |
| Psoriasis | 04 | 04 complete |
| Psoriatic arthritis | 02 | 01 complete/01 temporary |
| Systemic lupus erythematosus (SLE) | 02 | complete |
| Multiple sclerosis | 03 | complete |
| Crohn's disease | 06 | 05 complete/01 relapse |
| Ulcerative colitis | 01 | complete |
| <u>Autologous transplants</u> | | |
| Rheumatoid arthritis (RA) | 01 | temporary |
| Psoriasis | 03 | temporary |
| Systemic lupus erythematosus (SLE) | 04 | 3 complete/1 partial |
| Sjogren's syndrome | 02 | no remission |
| Crohn's disease | 02 | complete |



SCT in autoimmune disease

- ▶ 1996_European consensus meeting EULAR and EBMT on SCT in autoimmune disease (published 1997)
 - ▶ the hope that a ‘resetting’ of auto-aggressive immune responses might be possible
- ▶ 1996-First SCT in SSc patient
- ▶ Today more than 1500 patients transplanted for autoimmune disease worldwide





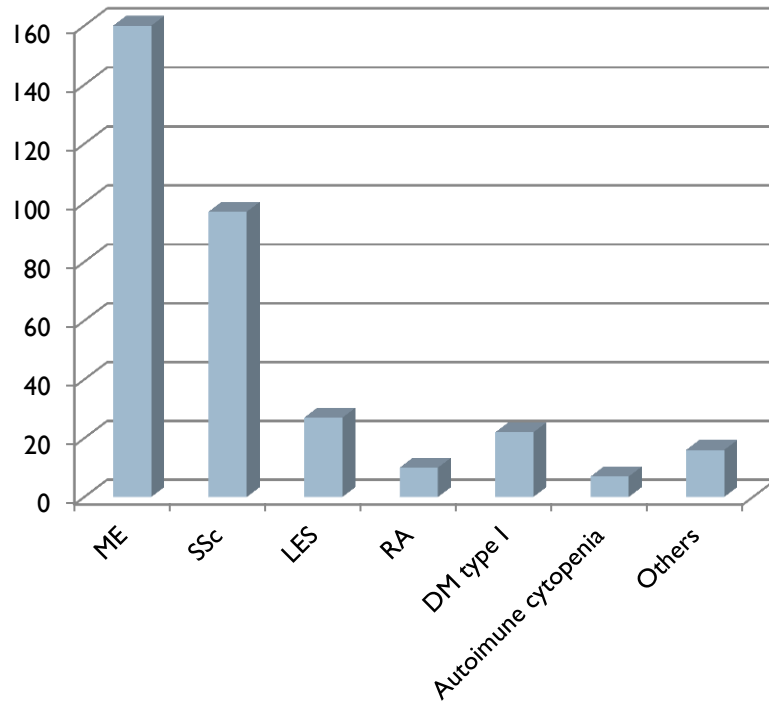
SCT in autoimmune disease

- ▶ Treatment of autoimmune disease
 - ▶ Immunesupression
 - ▶ Biologicals
- ▶ Indication for SCT in autoimmune diseases if patients:
 - ▶ diseases is severe enough to cause an increased risk of mortality or advanced and irreversible disability;
 - ▶ the disease has been unresponsive to conventional treatments;
 - ▶ the HSCT can be undertaken before irreversible organ damage, so that significant clinical benefit can be achieved.



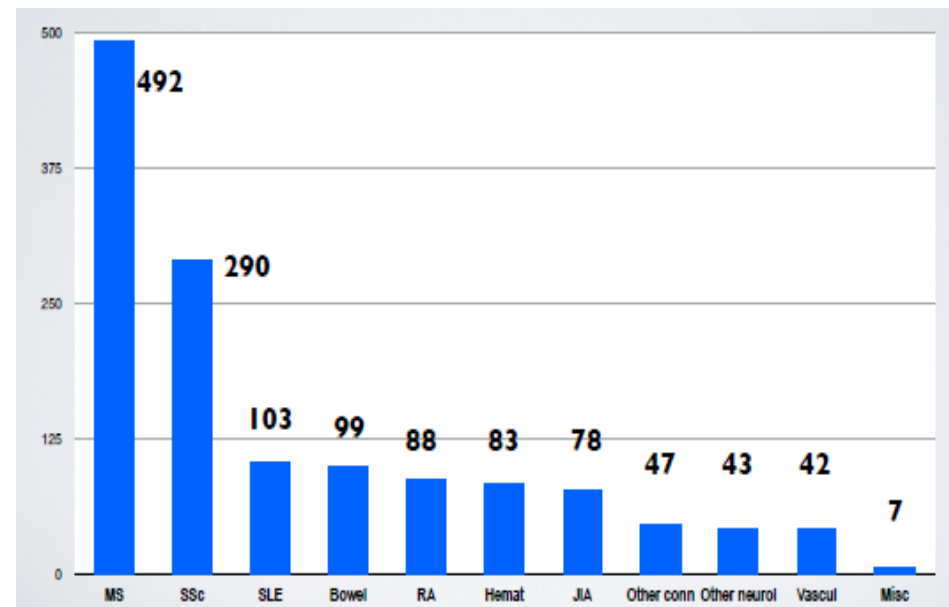
SCT for AID

North and South America



Pasquini MC et al, BBMT e-pub 2012

Europe



D. Farge EBMT 2012



SCT in Auto-Immune Diseases

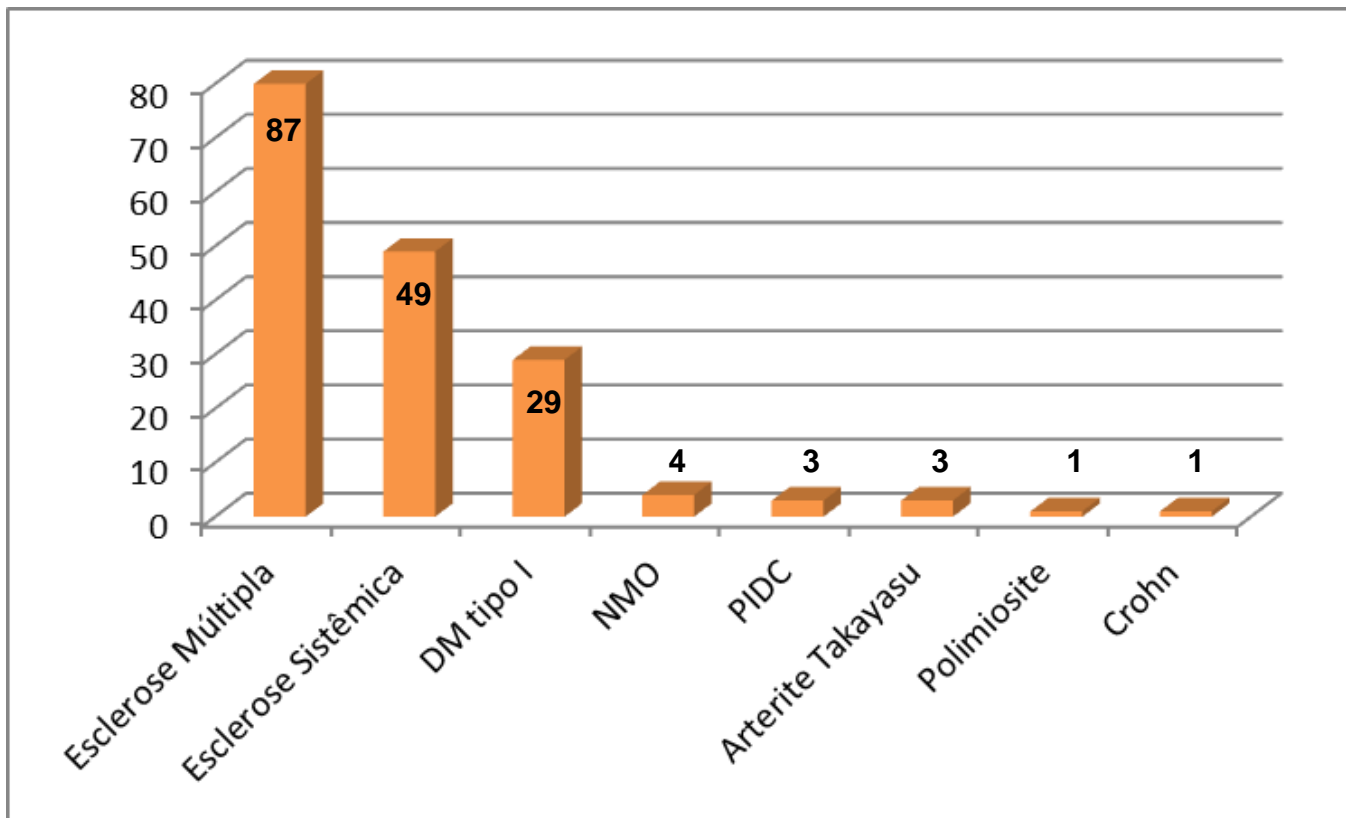
SCT in autoimmune disease: first approved trials in Brazil

| | Inclusion Criteria | Conditioning | Follow up |
|--------------------|---|---------------------|---|
| SLE (Lupus) | Nephritis, vasculitis, cytopenias refractory to IS, catastrophic anti-phospholip syndrome | Cy 200 mg/kg ATG | Disease activity TRM Immunerecovery |
| Multiple Sclerosis | Progressive forms refractory to IFN and EDSS 3,0 and 6,5 | BEAM + ATG | EDSS, MRI Immunerecovery TRM |
| Systemic Sclerosis | Duration of disease < 4 y Pulmonary disease refractory to IS | Cy 200 mg/kg ATG | Pulmonary function Immunerecovery TRM |



SCT in Autoimmune Disease

N= 177





SCT in Auto-Immune Diseases

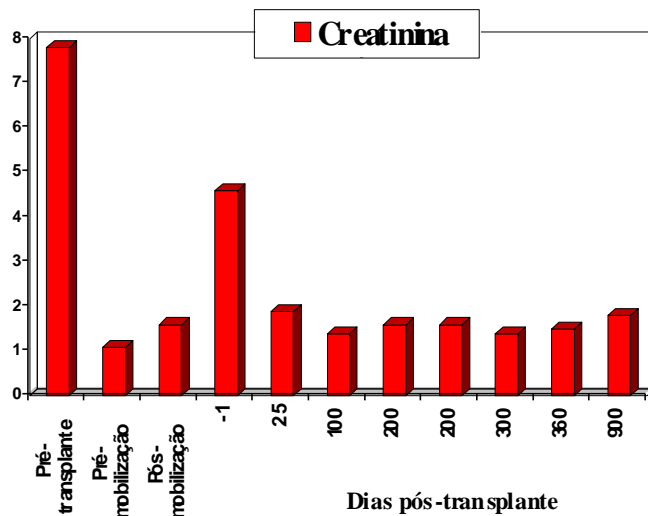
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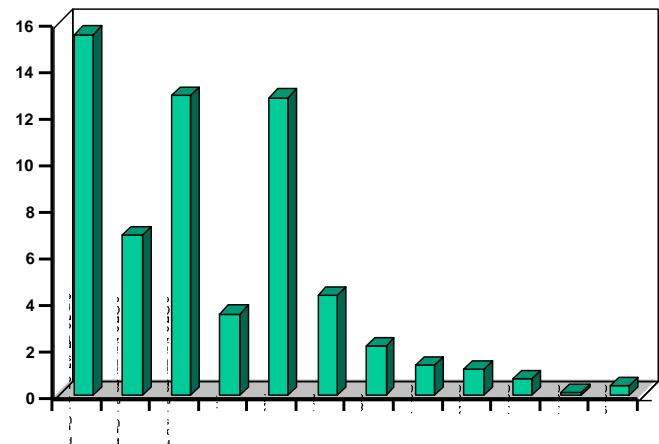
Before SCT



LUPUS

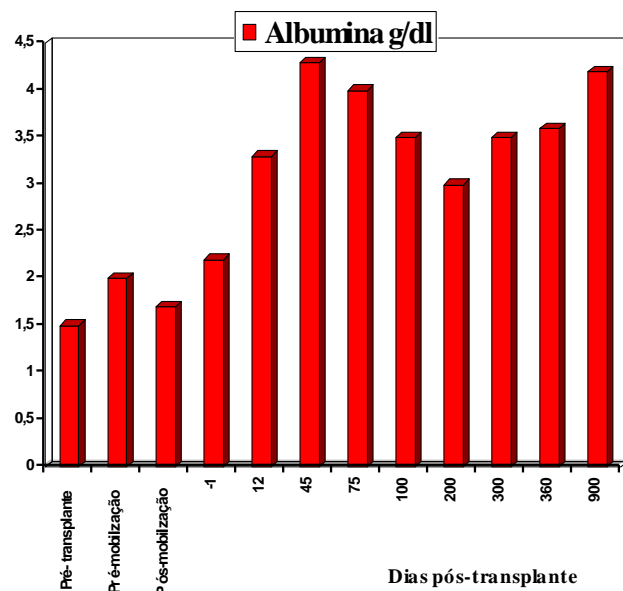
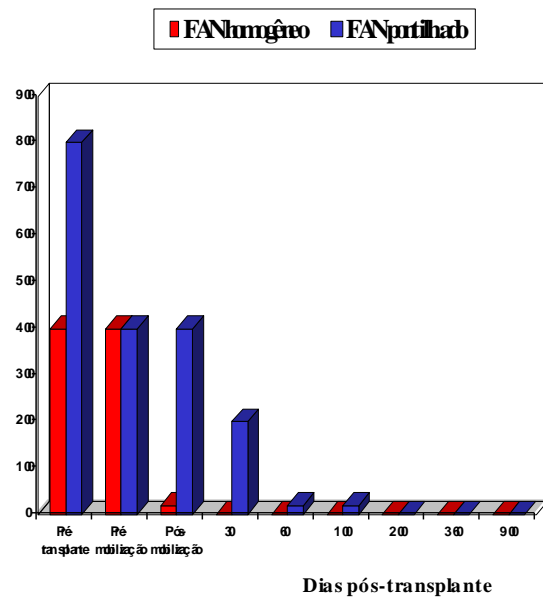


Proteinúria g/24hs



After SCT

PROF. DR. MARCOS FELIPE SILVA DE SA
 SUPERINTENDEnte
 PROF. DR. MARCO ANTONIO ZILGO
 CHEFE DO DEPTO DE CLINICA MEDICA
 PROF. DR. JÚLIO CÉSAR VOLTARELLI
 COORDENADOR DE T.M.O.
 APOIO FAEPA UNHO/1995





SCT in Lupus

- ▶ **6 patients**
 - ▶ 2 treatment free for more than 5 years in remission
 - ▶ 4 patients died of complications of diseases
- ▶ **New protocol started 2013 with a combination of chemotherapy + Rituximab and stem cell rescue**





SCT in Auto-Immune Diseases

SCT in autoimmune disease: first approved trials in Brazil

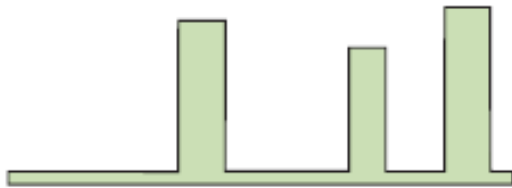
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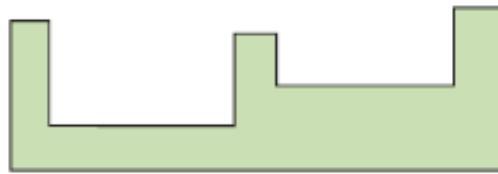


Multiple Sclerosis

Relapsing-remitting



Progressive forms

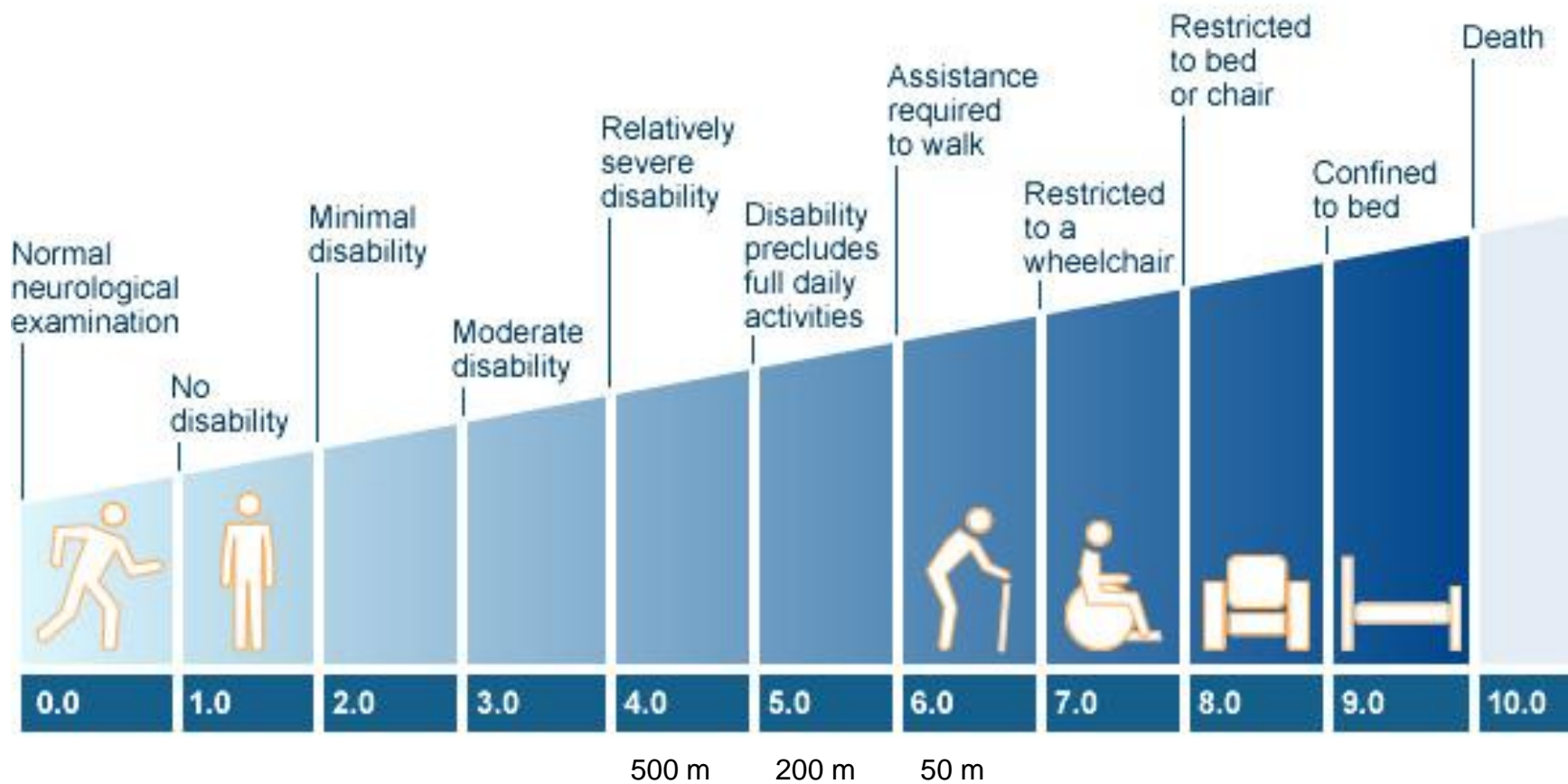


Compston & Coles, Lancet 2002





Expanded Disability Status Scale





MS: EBMT database



MS: EBMT database (n=503)

| | |
|--|---------------------|
| Male / Female (%) | 42 / 58 |
| Median age at transplant (in years) | 36 (12-65) |
| Median time from diagnosis to transplant (in years) | 6 (<1-34) |
| MS type (n =422) | |
| Secondary progressive | 204 (48) |
| Relapsing Remitting | 103 (21) |
| Primary progressive | 92 (18) |
| Progressive Relapsing | 23 (5) |
| Conditioning regimen (n=419) | |
| BEAM + ATG | 198 (47) |
| BEAM alone | 19 (4) |
| BEAM, missing ATG info | 77 (15) |
| Cyclo + ATG | 75 (18) |
| Cyclo + Thiotepa | 4 (8) |
| Other | 46 (9) |





SCT for MS in Brazil

▶ Inclusion Criteria

- ▶ MS diagnosis based on Poser criteria > 1 year
- ▶ Age 18 to 60 years
- ▶ Relapsing-remitting MS
- ▶ Primary or secondary progressive MS
- ▶ EDSS: 3,0 – 6,5
- ▶ Disease progression over the previous 6 months
 - ▶ At least 1,0 point deterioration in EDSS (3,0 – 6,0)
 - ▶ At least 0,5 points when EDSS between 6,0 and 6,5

Project approved by the local ethical committees and the National Investigational Review Board (CONEP) Ministry of Health





SCT for MS in Brazil

- ▶ **Transplant Protocol**
 - ▶ SCT mobilization –
 - ▶ Cyclophosphamide 2,0 gr/m² + G-CSF + Prednisone
 - ▶ Conditioning
 - ▶ BEAM + hATG + G-CSF + Prednisone

- ▶ **N= 21 patients**
 - ▶ EDSS \geq 6,0 in 81% of the patients
 - ▶ 3 early deaths
 - ▶ Study interrupted
 - ▶ Conditioning switched to Cy 200 + rATG 4,5 mg/kg





SCT for MS in Brazil

| Condition | Total | BEAM/ATG =20 | Cy/ATG = 21 | P-value |
|-----------------------|-------------|---------------|-------------|----------|
| EDSS | | | | |
| Worse | 14 (36,8%) | 8 (44,4%) | 6 (30%) | 0,596 |
| Stable | 9 (23,7%) | 3 (16,7%) | 6 (30%) | |
| Better | 15 (39,5%) | 7 (38,9%) | 8 (40%) | 0,357 |
| Stable and better | 24 (63,2%) | 10 (55,6%) | 14 (70%) | |
| MRI | | | | |
| Enhanced lesions | 0 | 0 | 0 | |
| Days at hospital | | 35,47 | 20,15 | < 0,0001 |
| Complications all | | 71,4% | 40% | 0,04 |
| Mortality | 3/41 (7,3%) | 3/21 (14,3%)* | 0/20 (0%) | |
| Event Free Survival** | | 47,2% | 70% | |
| Median Follow Up | | 6 years | 4 years | |

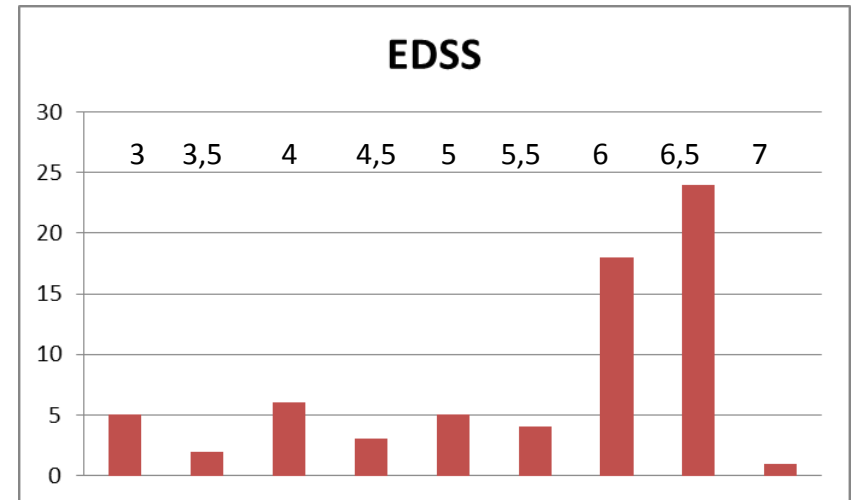
*Study interruption criteria: mortality > 10%

** stable or decreasing EDSS, no new lesions MRI, no relapse



SCT for MS in Brazil

- ▶ 66 patients with Cy + ATG
- ▶ Med Age: 38 (19-59)
- ▶ Med EDSS: 6,0
- ▶ Time initial and SCT: 8,7 years
- ▶ Med follow up 3 years
- ▶ Toxicity:
 - ▶ Common CMV reactivation
 - ▶ FUO
 - ▶ Pneumonia
 - ▶ Urinary tract infection
- ▶ Transplant related mortality
 - ▶ Zero!!



| MS type | Med years | Min | Max |
|---------|-----------|-----|------|
| Total | 8,7 | 0,5 | 31,5 |
| RR | 6,0 | 0,5 | 20,2 |
| PP | 7,2 | 3,3 | 10,2 |
| SP | 10,3 | 4,0 | 31,5 |



SCT for MS in Brazil

▶ Response definitions:

- ▶ Stable: stable EDSS without new MRI lesions, without any treatment after SCT
- ▶ Progression: 0,5 increase in EDSS, new lesions MRI and new treatment after SCT
- ▶ Improvement: any decrease of EDSS

| | ALL (66) | % | RR (27) | % | PP (4) | % | SP (35) | % |
|----------------|-----------------|----------|----------------|----------|---------------|----------|----------------|----------|
| Improve | 25 | 36,7 | 14 | 51 | 2 | | 13 | 37 |
| Worser | 17 | 25,1 | 2 | 18 | 1 | | 14 | 40 |
| Stable | 26 | 38,2 | 11 | 31 | 1 | | 8 | 23 |
| I+S | 51 | 74,9 | 25 | 82 | 3 | | 21 | 60 |
| EDSS | | | | | | | | |
| Med | 6,0 | | 5,5 | | 6,5 | | 6,0 | |

- One single patient with new MRI lesion
- 4 patients needed further treatment after SCT very easily treated



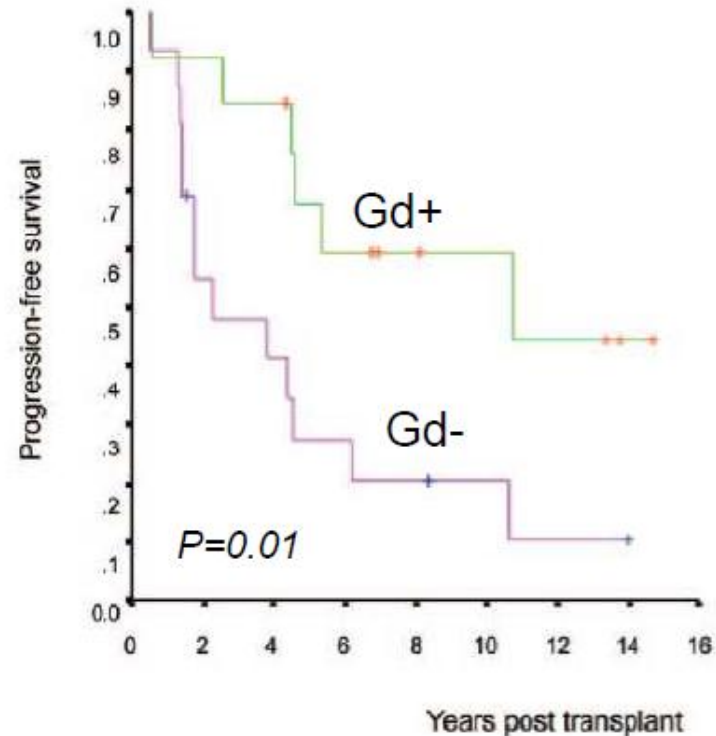


MS: the greek experience

Long-term results of stem cell transplantation for MS : A single-center experience

A. Fassas, V.K. Kimiskidis, I. Sakellari, et al.
Neurology 2011;76;1066

- n=35
- Age at HSCT =40 (19-54)
- FU (yrs) = 11.3 (1.6-14.6)
- Interval to HSCT = 7 (1-18)
- MS form at HSCT
 - SP=19, RP=3, RR=1, PP=1, Malignant=1
- EDSS at baseline= 6 (4.5-8)
- HSCT technology:
 - BEAM/ATG (15),
 - BEAM/ATG/CD34 sel (10)
 - Oral Busulphan (10)



Progression-free survival by pretransplant MRI activity (presence of gadolinium-enhancing, new, or enlarging T2 lesions)

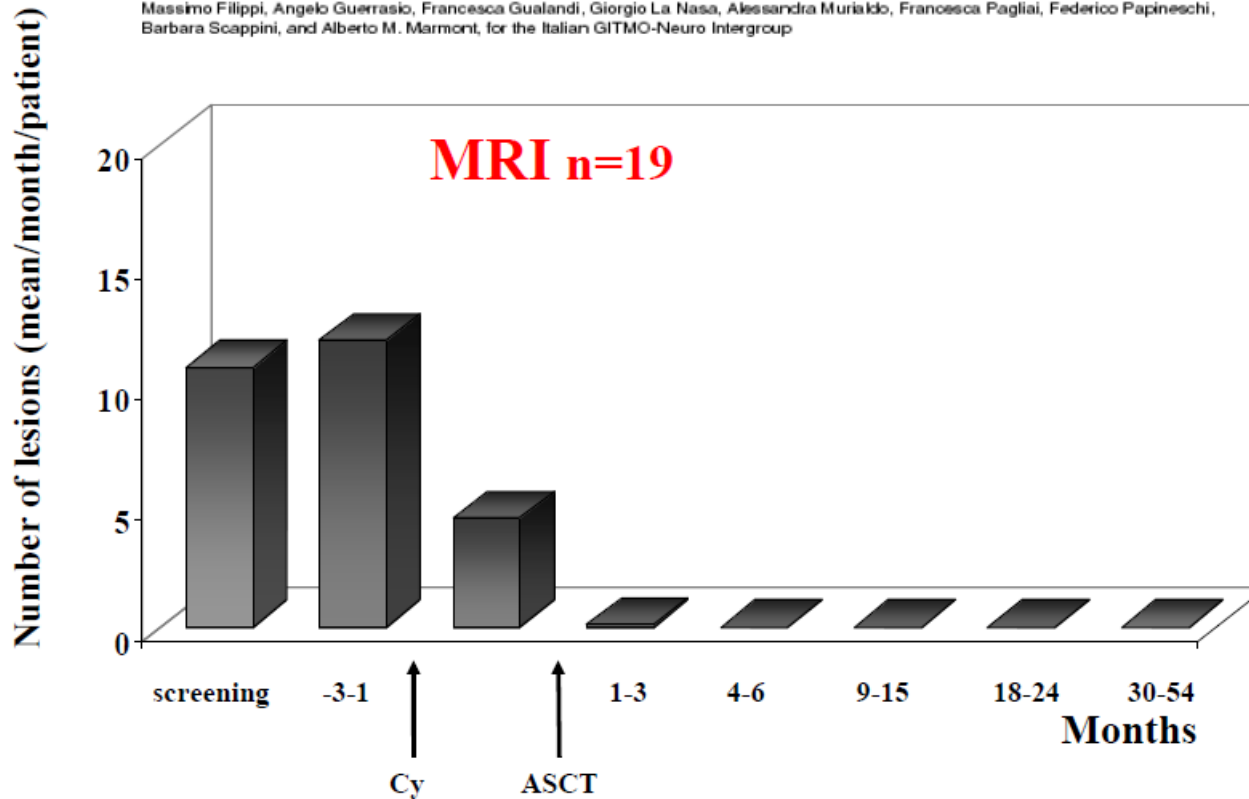


MS: the Italian Experience

TRANSPLANTATION

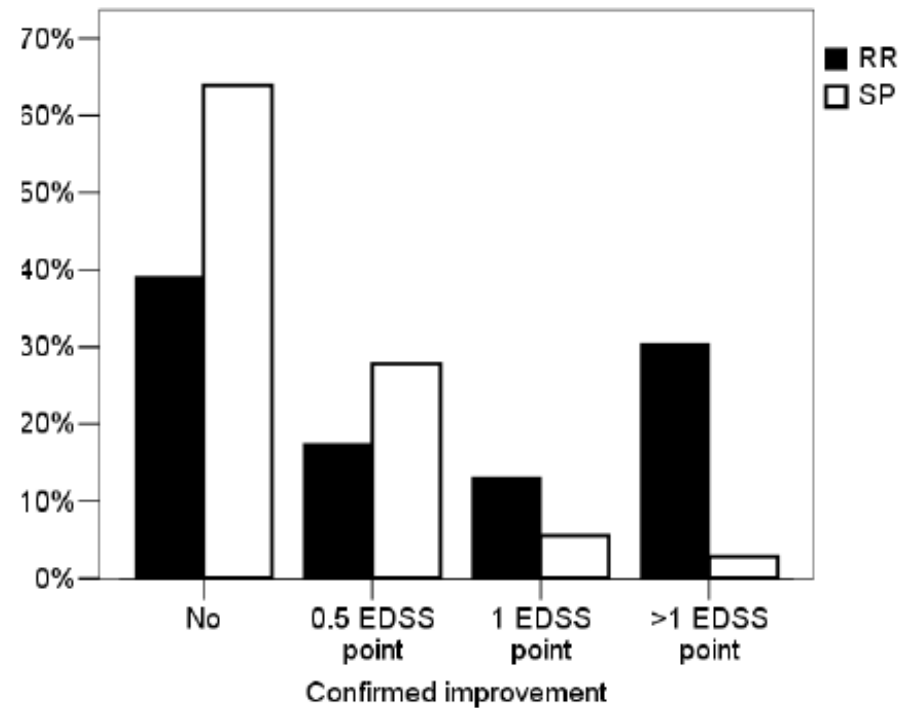
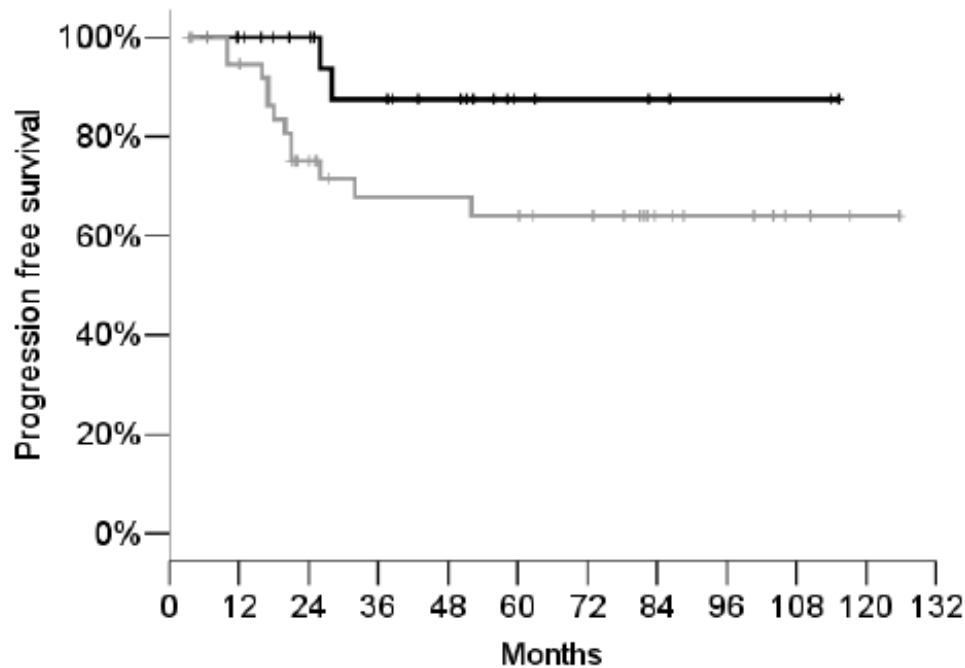
Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life

Riccardo Saccardi, Gian Luigi Mancardi, Alessandra Solari, Alberto Bosi, Paolo Bruzzi, Paolo Di Bartolomeo, Amedea Donelli, Massimo Filippi, Angelo Guerrasio, Francesca Gualandi, Giorgio La Nasa, Alessandra Muriakdo, Francesca Pagliai, Federico Papineschi, Barbara Scappini, and Alberto M. Marmor, for the Italian GITMO-Neuro Intergroup





MS: the Italian Experience





**▶ LONG TERM OUTCOMES AFTER
AUTOLOGOUS HEMATOPOIETIC CELL
TRANSPLANTATION FOR MULTIPLE
SCLEROSIS – A joint study from the Center for
International Blood and Marrow Research
(CIBMTR) and from the European Group for
Blood and Marrow Transplantation (EBMT)**



Van Bekkum award – EBMT 2013





MS – CIBMTR and EBMT

| Characteristics | N=281 (%) |
|------------------------|------------------|
| EBMT | 170 (60) |
| CIBMTR | 111 (40) |
| Centers (EBMT/CIBMTR) | 25 (17/8) |
| Age, median (range) | 37 (14-65) |
| Age<40y | 171 (61) |
| Female | 164 (58) |

N=30 – Ribeirão Preto



MS – CIBMTR and EBMT

| Characteristics | N=281 (%) |
|--|------------------|
| EDSS prior to mobilization, median (range) | 6.5 (1.5-9.5) |
| Median time from diagnosis to transplant, months | 82 (1-413) |
| ≥2 Prior lines of therapies | 171 (61) |
| Disease Status at Mobilization | |
| Relapsing Forms | 46 (16) |
| Progressive Forms | 235 (84) |

Muraro P et al – EBMT 2013





MS – CIBMTR and EBMT

- ▶ Median follow up
 - ▶ 6,6 years

- ▶ Progression free survival
 - ▶ At 5 years – 49%

- ▶ Overall Survival
 - ▶ At 5 years – 93%

Muraro P et al – EBMT 2013





Univariate analysis for MS Progression

| Variable | HR (95% CI) | P-value |
|---------------------------------------|-------------------------|-------------|
| CIBMTR vs. EBMT | 1.1 (0.81-1.5) | 0.50 |
| Age | 1.02 (1.0-1.04) | 0.02 |
| Fem vs. Male | 0.92 (0.67-1.25) | 0.60 |
| Disease duration | 1.0 (0.99-1.05) | 0.26 |
| Conditioning Intensity | | 0.44 |
| Int vs. low | 0.77 (0.51-1.17) | |
| High vs. low | 0.88 (0.54-1.47) | |
| ATG | 1.27 (0.83-1.95) | 0.27 |
| Other regimens vs. BEAM | 1.08 (0.72-1.64) | 0.70 |
| Progressive vs. Relapsing | 1.72 (1.15-2.57) | 0.01 |
| Chemoembolization | 1.02 (0.58-1.82) | 0.94 |
| >2 vs. 1-2 lines of therapy | 1.46 (1.06-2.00) | 0.02 |
| 2001-2006 vs. 1995-2000 | 1.18 (0.85-1.64) | 0.34 |



SCT in Auto-Immune Diseases

SCT in autoimmune disease: first approved trials in Brazil

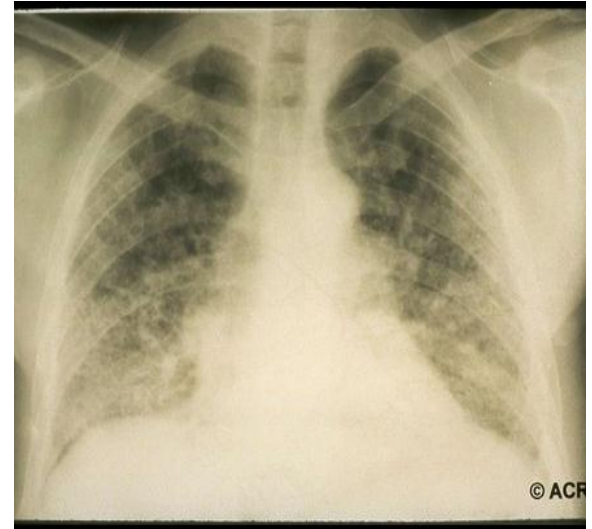
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Systemic Sclerosis

- ▶ Prevalence: 20 to 75/100.000
- ▶ 30-60 years
- ▶ More prevalent in women
- ▶ Cardiac, pulmonar, gastrointestinal, skin and kidney



- ▶ Severe forms:
 - ▶ mortality of 50% in 5 years





International Data on SCT in SS

- ▶ **2004: Farget et al. (Ann Rheumatic Dis)**
 - ▶ 57 patients
 - ▶ Skin improvement in 70%
 - ▶ Stabilization of pulmonary function
 - ▶ 30% relapse

- ▶ **2007: Vonck et al. (Ann Rheumatic Dis)**
 - ▶ 26 patients
 - ▶ Skin improvement in 81%
 - ▶ Stabilization of pulmonary function
 - ▶ 96% overall survival 5 years
 - ▶ 64% progression free survival





SCT for SSc in Brazil and Chicago

▶ Inclusion Criteria

- ▶ Age < 60 years
- ▶ Progressive disease
- ▶ Diffuse skin involvement or
- ▶ Severe visceral involvement

▶ Exclusion criteria

- ▶ Advanced pulmonary fibrosis (DLCO<40%)
- ▶ Severe pulmonary hypertension (PAP>60mmHg)
- ▶ Cardiac involvement (LVEF < 50%)





SCT for SSc in Brazil and Chicago

▶ N = 90 pts (31 Brazil, 59 Chicago)

| | Patients (n=90) |
|--|-----------------|
| Median age, years | 42 (16-71) |
| Sex, female | 73 (81%) |
| Ethnicity | |
| White | 70 (78%) |
| Black | 11 (12%) |
| Hispanic | 5 (6%) |
| Biracial | 3 (3%) |
| Native American | 1 (1%) |
| Median disease duration from diagnosis to HSCT, months | 25 (2-156) |
| History of Raynaud's phenomena | 83 (92%) |
| Median modified Rodnan skin score | 24 (3-47) |
| Diffuse systemic sclerosis | 72 (80%) |

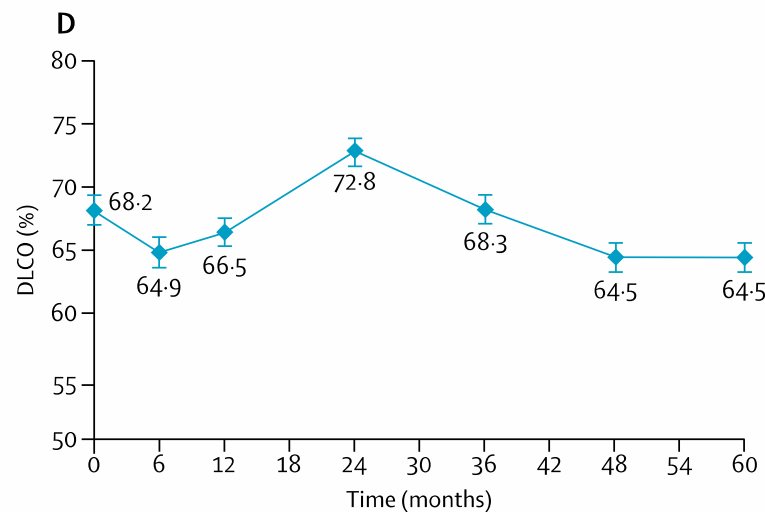
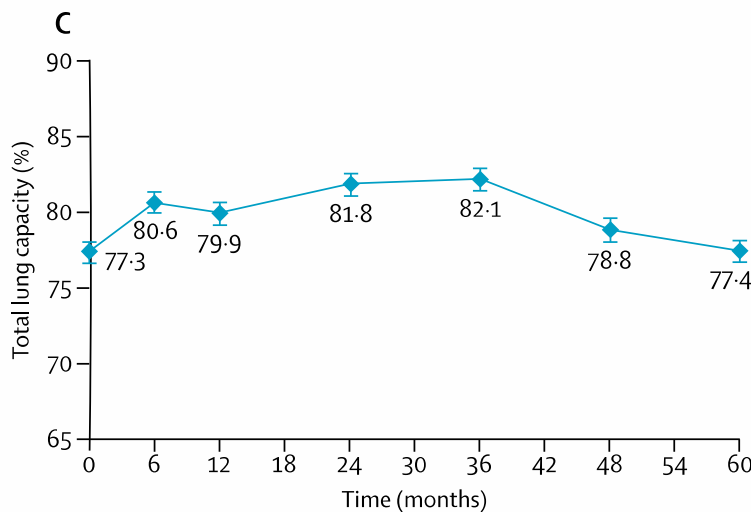
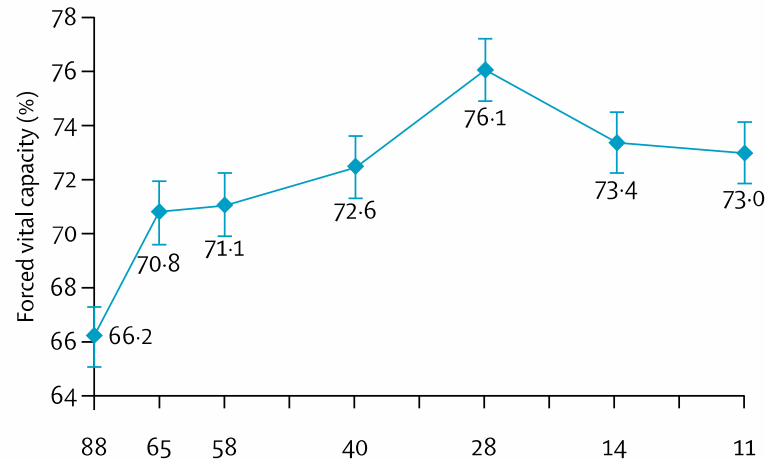
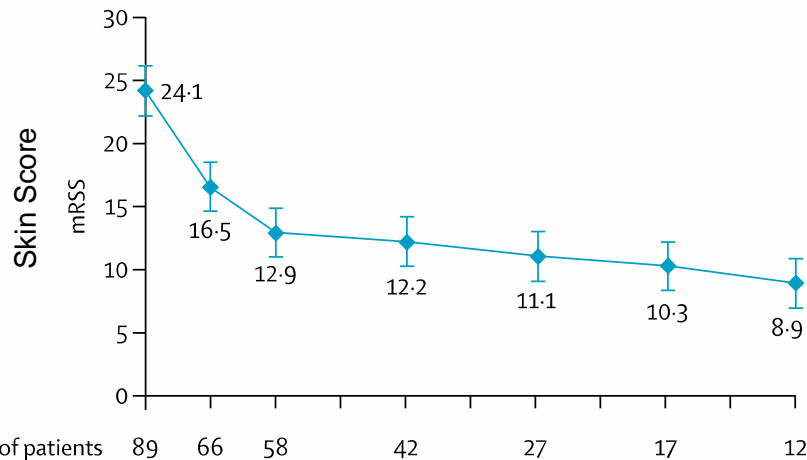


SCT for SSc in Brazil and Chicago

| | |
|--|-----------|
| Diffuse systemic sclerosis | 72 (80%) |
| Gastrointestinal track disorders | 81 (90%) |
| Gastro-oesophageal reflux disease | 51 (63%) |
| Patulous esophagous | 52 (64%) |
| Gastrointestinal antral vascular ectasia | 5 (6%) |
| Small bowel involvement | 3 (4%) |
| Total parenteral nutrition | 1 (1%) |
| Abnormal lung involvement on imaging | 73 (81%) |
| Interstitial lung disease | 73 (100%) |
| Nodules or micronodules | 4 (5%) |
| Bronchiectasis | 7 (10%) |
| Honeycombing | 2 (3%) |
| Oxygen dependency | 2 (3%) |

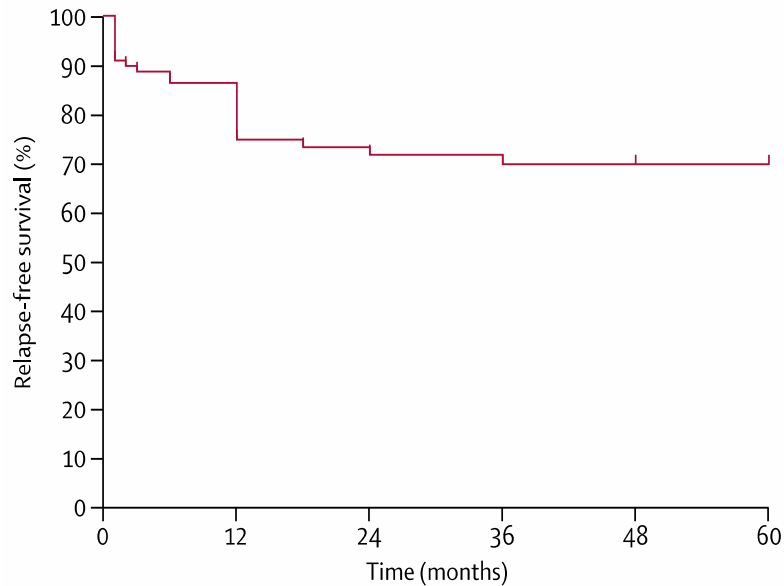


SCT for SSc in Brazil and Chicago



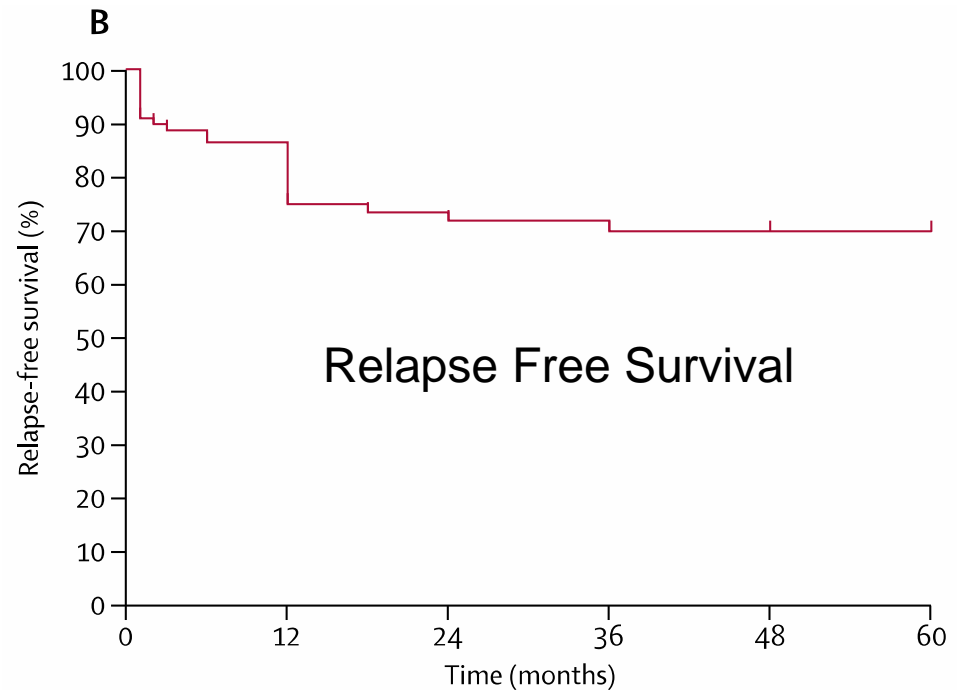


SCT for SSc in Brazil and Chicago



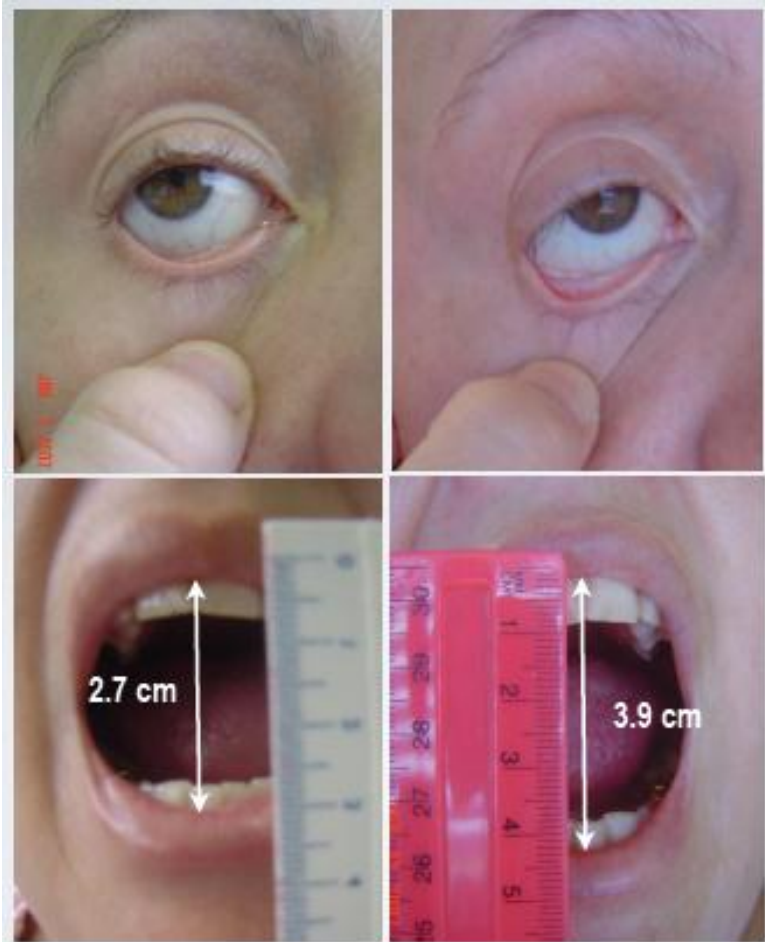
5 patients died early (TRM 6%)
4 cardiac complications
1 sepsis
13 patients relapsed
8 died of disease

Overall Survival = 78% at 5 years





SCT in SSc – Cutaneous involvement



Pre

Day + 40



Pre
(3,5cm)

Day +90
(4,7cm)

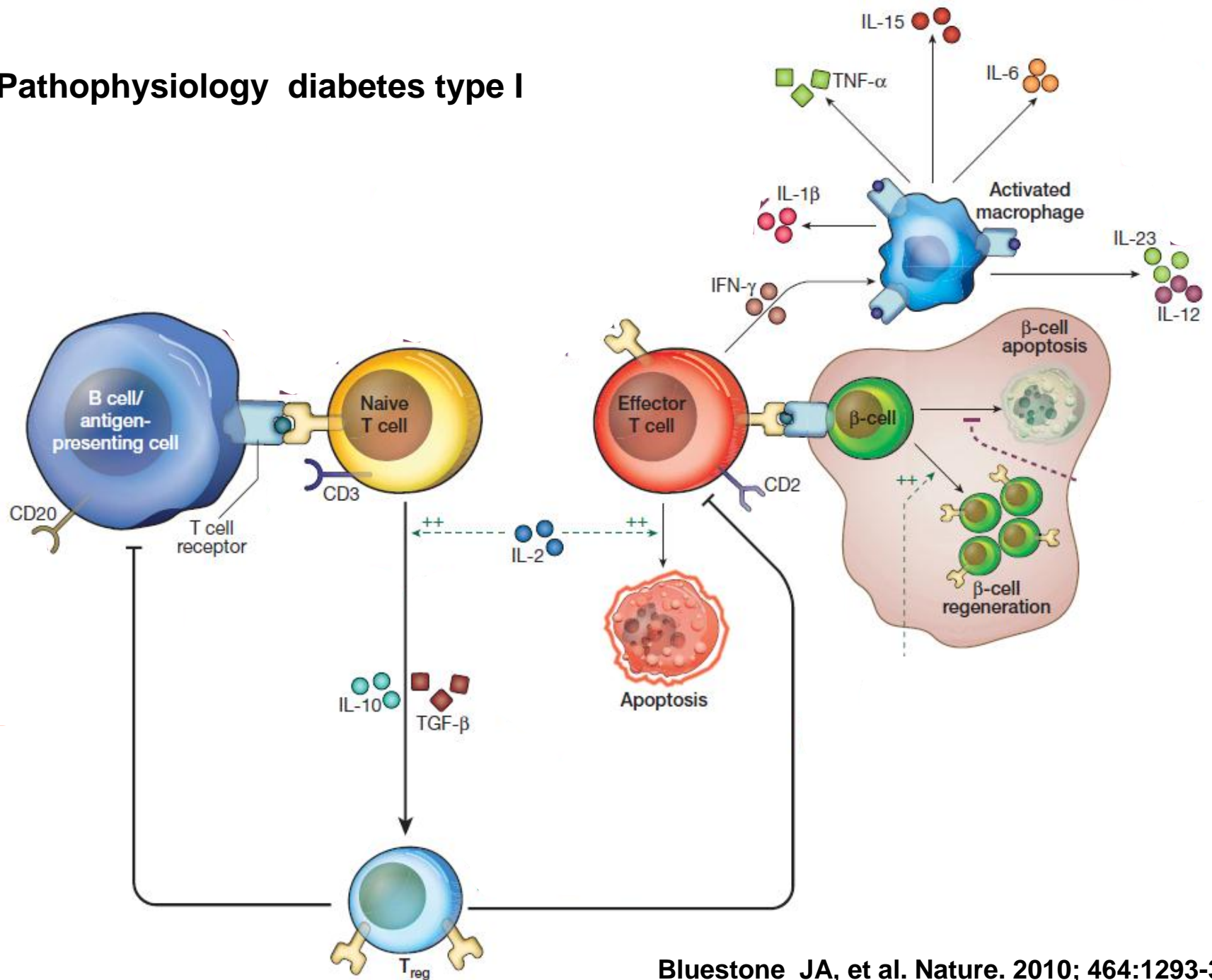




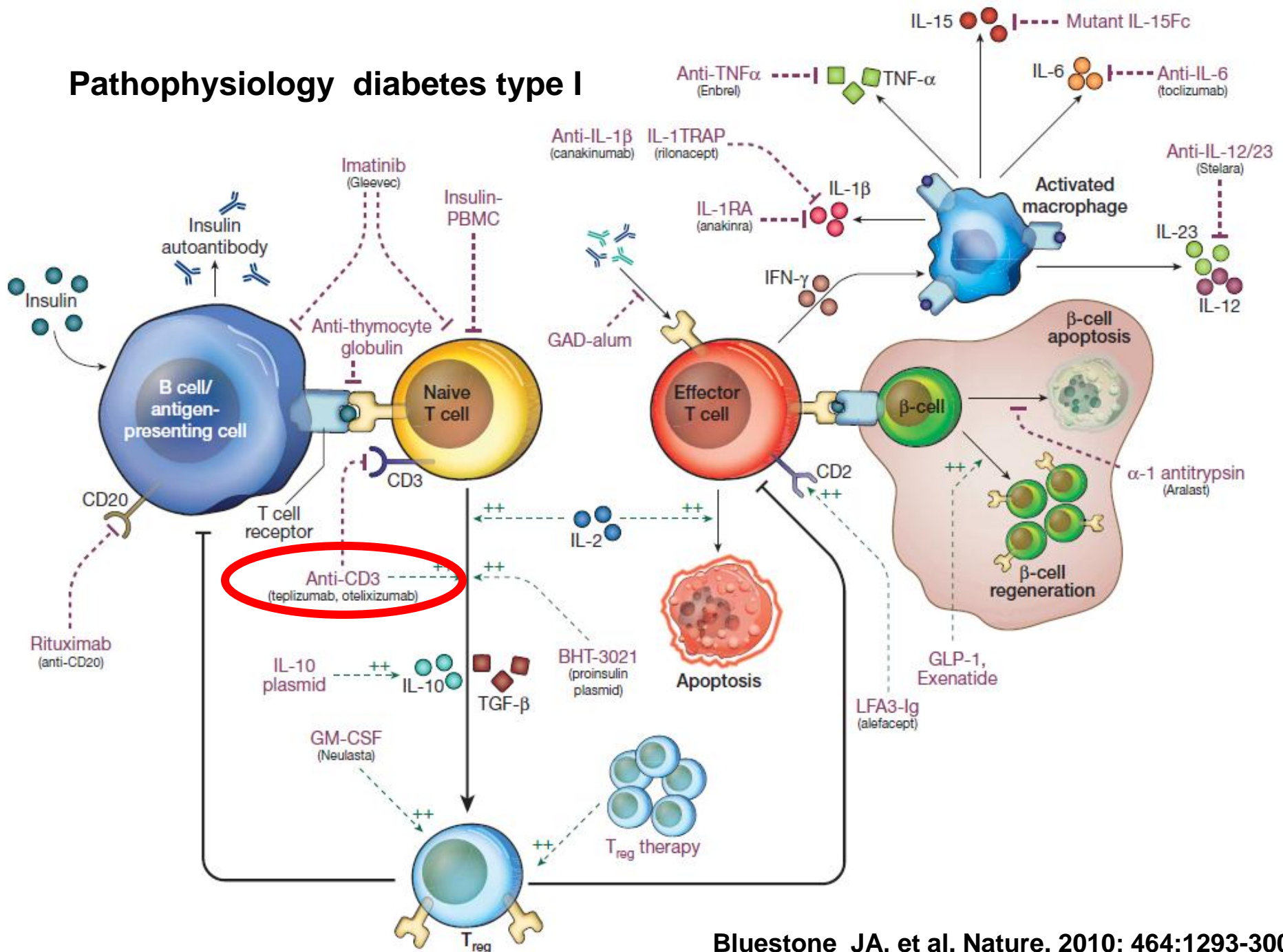
Diabetes Mellitus type I



Pathophysiology diabetes type I



Pathophysiology diabetes type I





Diabetes Mellitus type I

- ▶ Autoimmune Disease
- ▶ Previous trials
 - ▶ immunosuppression
 - ▶ Prednisone
 - ▶ Cyclosporine
 - ▶ OKT3
 - ▶ Azathioprine
 - ▶ Vaccination
 - ▶ GAD treatment





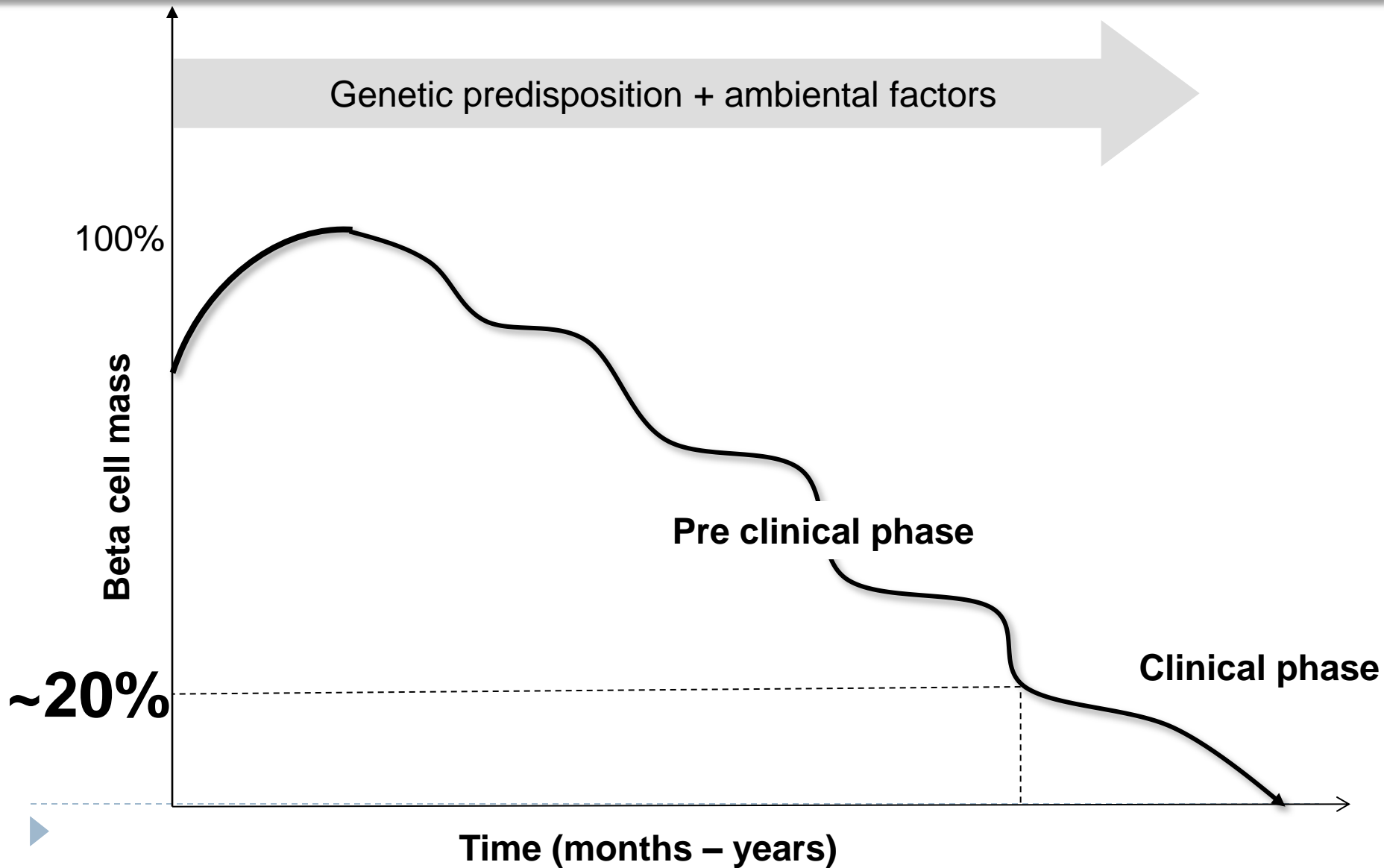
Diabetes Mellitus type I

- ▶ Autoimmune Disease
- ▶ Previous trials
 - ▶ Immunossuppression: never insulin free
 - ▶ Prednisone
 - ▶ Cyclosporine
 - ▶ OKT3
 - ▶ Azatioprine
 - ▶ Vaccination: never insulin free
 - ▶ GAD treatment: randomized trial negative





Genetic predisposition + ambiantal factors





Genetic predisposition + ambiantal factors

100%

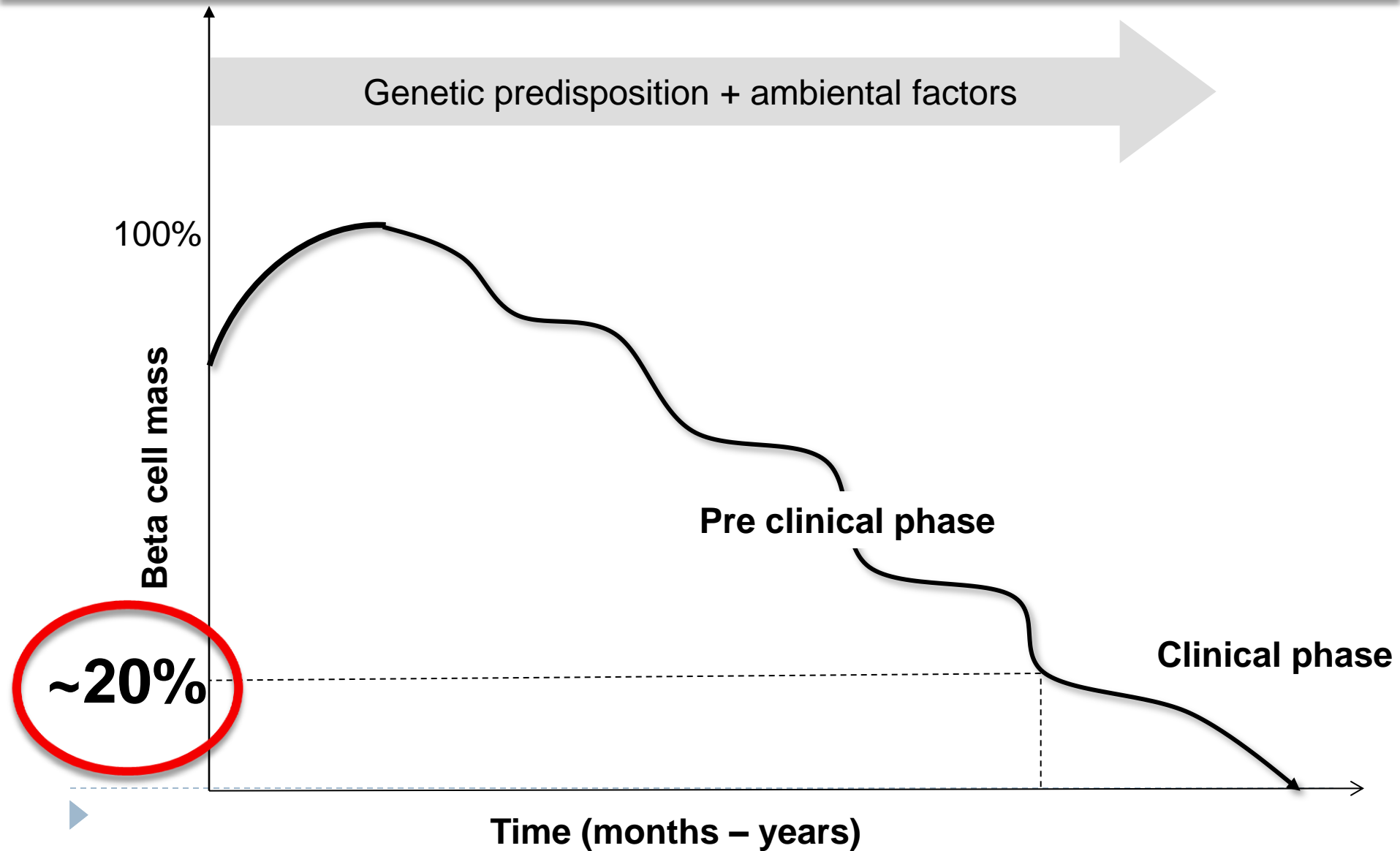
Beta cell mass

~20%

Pre clinical phase

Clinical phase

Time (months – years)





SCT in autoimmune disease

- ▶ Treatment of autoimmune disease
 - ▶ Immunesupression
 - ▶ Biologicals
- ▶ Indication for SCT in autoimmune diseases if patients:
 - ▶ diseases is severe enough to cause an increased risk of mortality or advanced and irreversible disability;
 - ▶ the disease has been unresponsive to conventional treatments;
 - ▶ the HSCT can be undertaken before irreversible organ damage, so that significant clinical benefit can be achieved.



SCT in type I Diabetes Mellitus

▶ Inclusion Criteria

- ▶ Age 12 – 35 years
- ▶ No more than 4 weeks of diagnosis
 - ▶ Patient had to be transplanted within 6 weeks of diagnosis
- ▶ Anti-GAD positive

▶ Interruption criteria

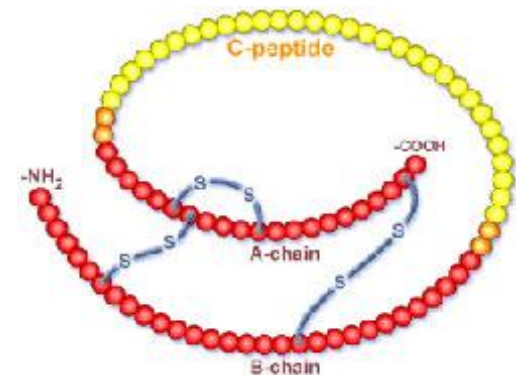
- ▶ 1 death





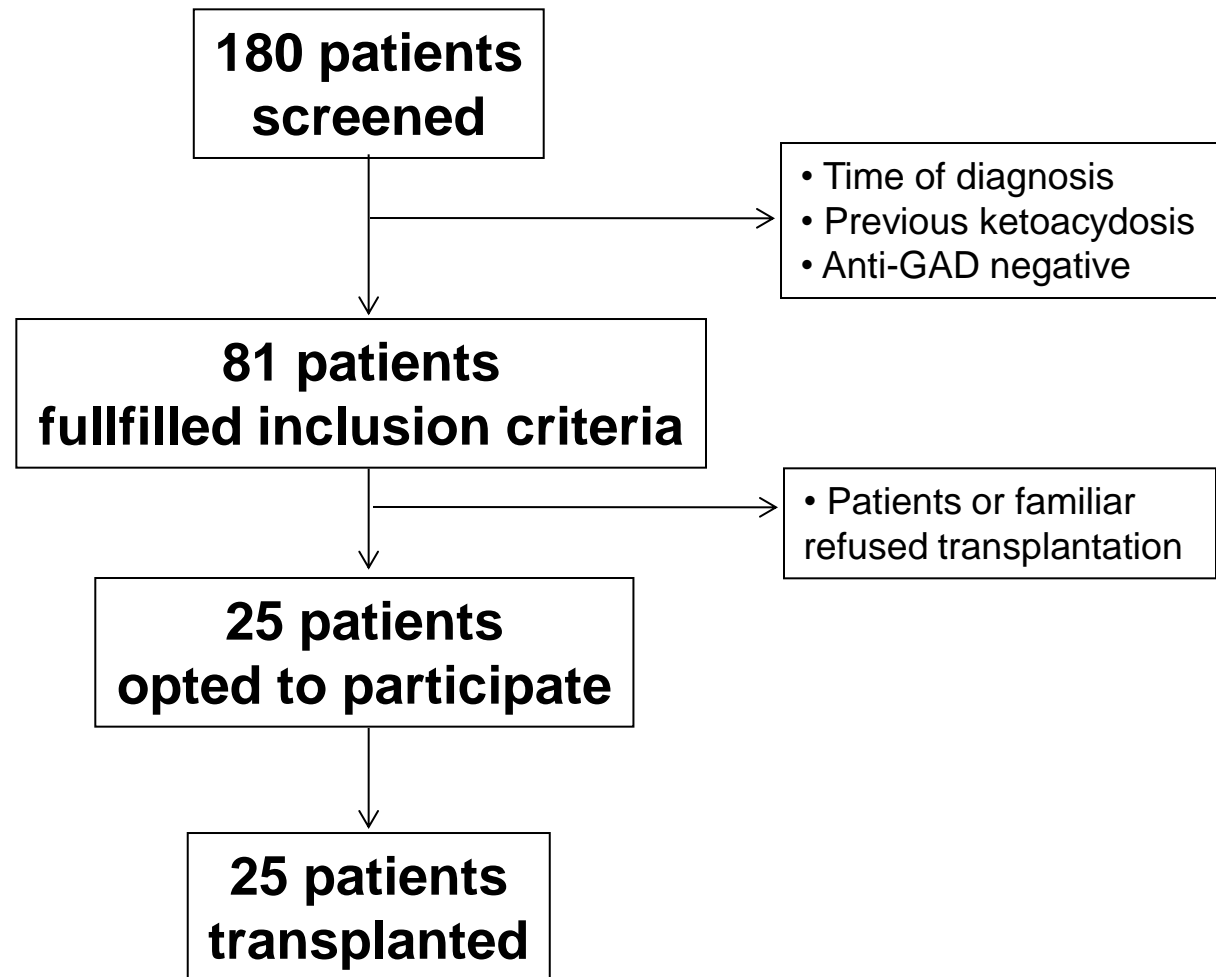
SCT in Diabetes Mellitus type I

- ▶ **Primary Endpoint**
 - ▶ C-peptide levels : 2 hrs. mixed meal tolerance test
- ▶ **Secondary Endpoints**
 - ▶ Morbidity and mortality SCT
 - ▶ Exogenous insulin requirement
 - ▶ Serum levels of Hemoglobin A_{1c}





SCT in Diabetes Mellitus type I





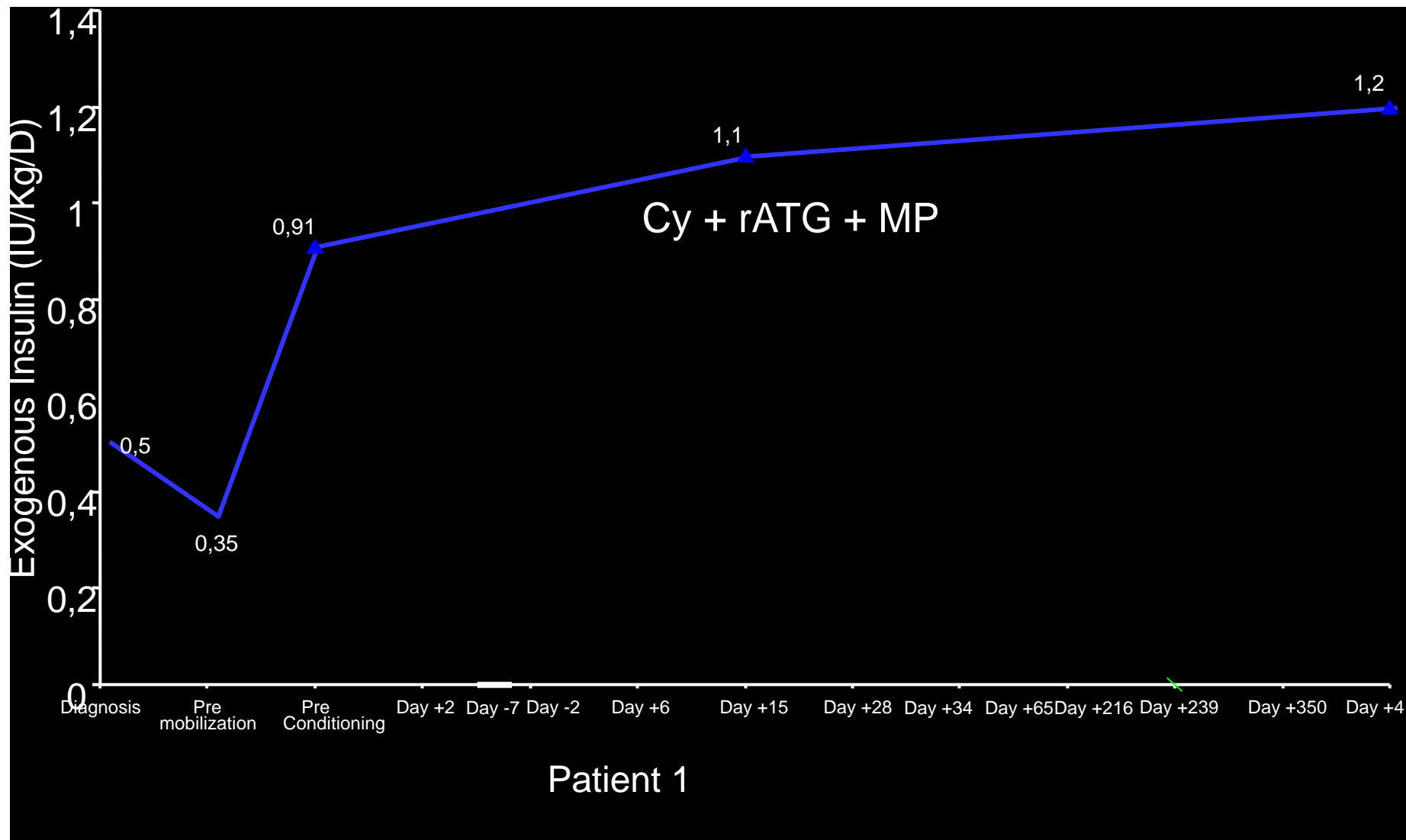
SCT in Diabetes Mellitus type I

| Condition | Mean |
|-------------------------------|--|
| Age | Median 18,4 (13 – 31) |
| Blood Glucose Levels | 398,6 mg/dl |
| GAD antibody | 24,9 U/mL |
| Time until mobilization | 37,7 days (24 – 56) |
| Duration of hospital stay | 18,6 days (15 -24 days) |
| CD34x10 ⁶ cells/kg | 10,52 x 10 ⁶ /kg (4,98 – 23,19) |
| Neutrophil engraftment | 9,3 days (8-11) |
| Platelet engraftment | 10,4 (0 – 18) |





SCT in Diabetes Mellitus type I





SCT in Diabetes Mellitus type I

▶ Inclusion Criteria

- ▶ Age 12 – 35 years
- ▶ No more than 4 weeks of diagnosis
 - ▶ Patient had to be transplanted within 6 weeks of diagnosis
- ▶ Anti-GAD positive

▶ Interruption criteria

- ▶ 1 death





SCT in Diabetes Mellitus type I

▶ Inclusion Criteria

- ▶ Age 12 – 35 years
- ▶ No more than 4 weeks of diagnosis
 - ▶ Patient had to be transplanted within 6 weeks of diagnosis
- ▶ No previous ketoacidosis
- ▶ Anti-GAD positive

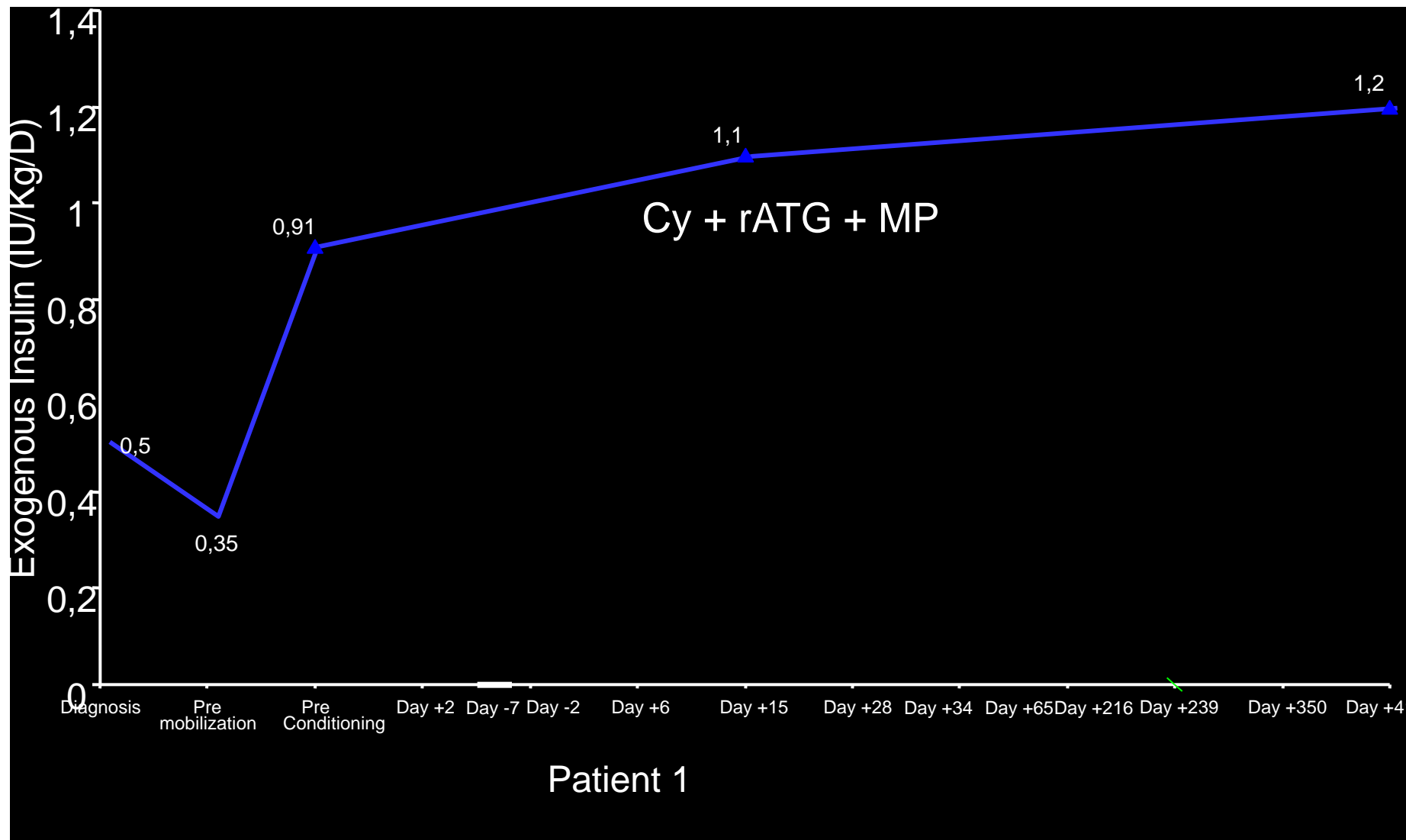
▶ Interruption criteria

- ▶ 1 death



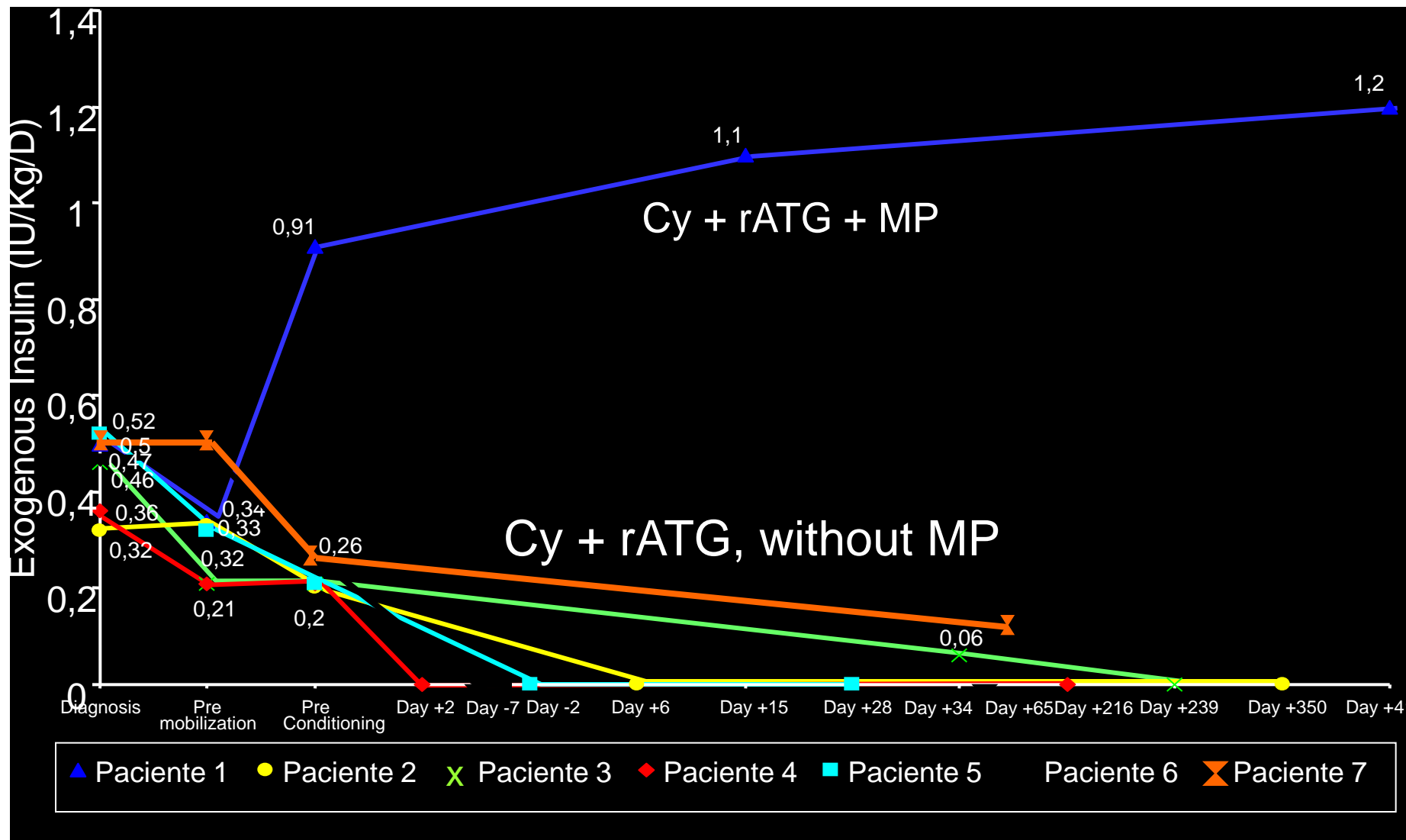


SCT in Diabetes Mellitus type I






SCT in Diabetes Mellitus type I





SCT in Diabetes Mellitus type I

| | Pre | 6m | 12m |
|----|---------|--------------|--------------|
| 1 | insulin | insulin | insulin |
| 2 | insulin | insulin-free | insulin-free |
| 3 | insulin | insulin-free | insulin-free |
| 4 | insulin | insulin-free | insulin-free |
| 5 | insulin | insulin-free | insulin-free |
| 6 | insulin | insulin-free | insulin-free |
| 7 | insulin | insulin | insulin |
| 8 | insulin | insulin-free | insulin-free |
| 9 | insulin | insulin-free | insulin-free |
| 10 | insulin | insulin | insulin-free |
| 11 | insulin | insulin-free | insulin-free |
| 12 | insulin | insulin-free | insulin-free |
| 13 | insulin | insulin-free | insulin-free |
| 14 | insulin | insulin-free | insulin-free |
| 15 | insulin | insulin-free | insulin-free |
| 16 | insulin | insulin-free | insulin-free |
| 17 | insulin | insulin-free | insulin-free |
| 18 | insulin | insulin-free | insulin-free |
| 19 | insulin | insulin | insulin |
| 20 | insulin | insulin-free | insulin-free |
| 21 | insulin | insulin | insulin-free |
| 22 | insulin | insulin-free | insulin-free |
| 23 | insulin | insulin-free | insulin-free |
| 24 | insulin | insulin | insulin |
| 25 | insulin | insulin | insulin |

 patients using insulin
 patients insulin-free





SCT in Diabetes Mellitus type I

| | Pre | 6m | 12m | 18m | 24m |
|----|---------|--------------|--------------|--------------|--------------|
| 1 | insulin | insulin | insulin | insulin | insulin |
| 2 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 3 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 4 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 5 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 6 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 7 | insulin | insulin | insulin | insulin | insulin |
| 8 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 9 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 10 | insulin | insulin | insulin-free | insulin | insulin |
| 11 | insulin | insulin-free | insulin-free | insulin | insulin |
| 12 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 13 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 14 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 15 | insulin | insulin-free | insulin-free | insulin | insulin |
| 16 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 17 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 18 | insulin | insulin-free | insulin-free | insulin-free | insulin-free |
| 19 | insulin | insulin | insulin | insulin | insulin |
| 20 | insulin | insulin-free | insulin-free | insulin-free | insulin |
| 21 | insulin | insulin | insulin-free | insulin-free | insulin-free |
| 22 | insulin | insulin-free | insulin-free | insulin | insulin |
| 23 | insulin | insulin-free | insulin-free | insulin | insulin |
| 24 | insulin | insulin | insulin | insulin | |
| 25 | insulin | insulin | insulin | insulin | |

insulin patients using insulin
insulin-free patients insulin-free





SCT in Diabetes Mellitus type I

| | Pre | 6m | 12m | 18m | 24m | 30m | 36m |
|----|---------|--------------|--------------|--------------|--------------|--------------|--------------|
| 1 | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 2 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 3 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 4 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 5 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 6 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 7 | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 8 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 9 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 10 | insulin | insulin | insulin-free | insulin | insulin | insulin | insulin |
| 11 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin |
| 12 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 13 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 14 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 15 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin |
| 16 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 17 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 18 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin |
| 19 | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 20 | insulin | insulin-free | insulin-free | insulin-free | insulin | insulin | insulin |
| 21 | insulin | insulin | insulin-free | insulin-free | insulin-free | insulin | insulin |
| 22 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin |
| 23 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin |
| 24 | insulin | insulin | insulin | insulin | | | |
| 25 | insulin | insulin | insulin | insulin | | | |

insulin patients using insulin
insulin-free patients insulin-free



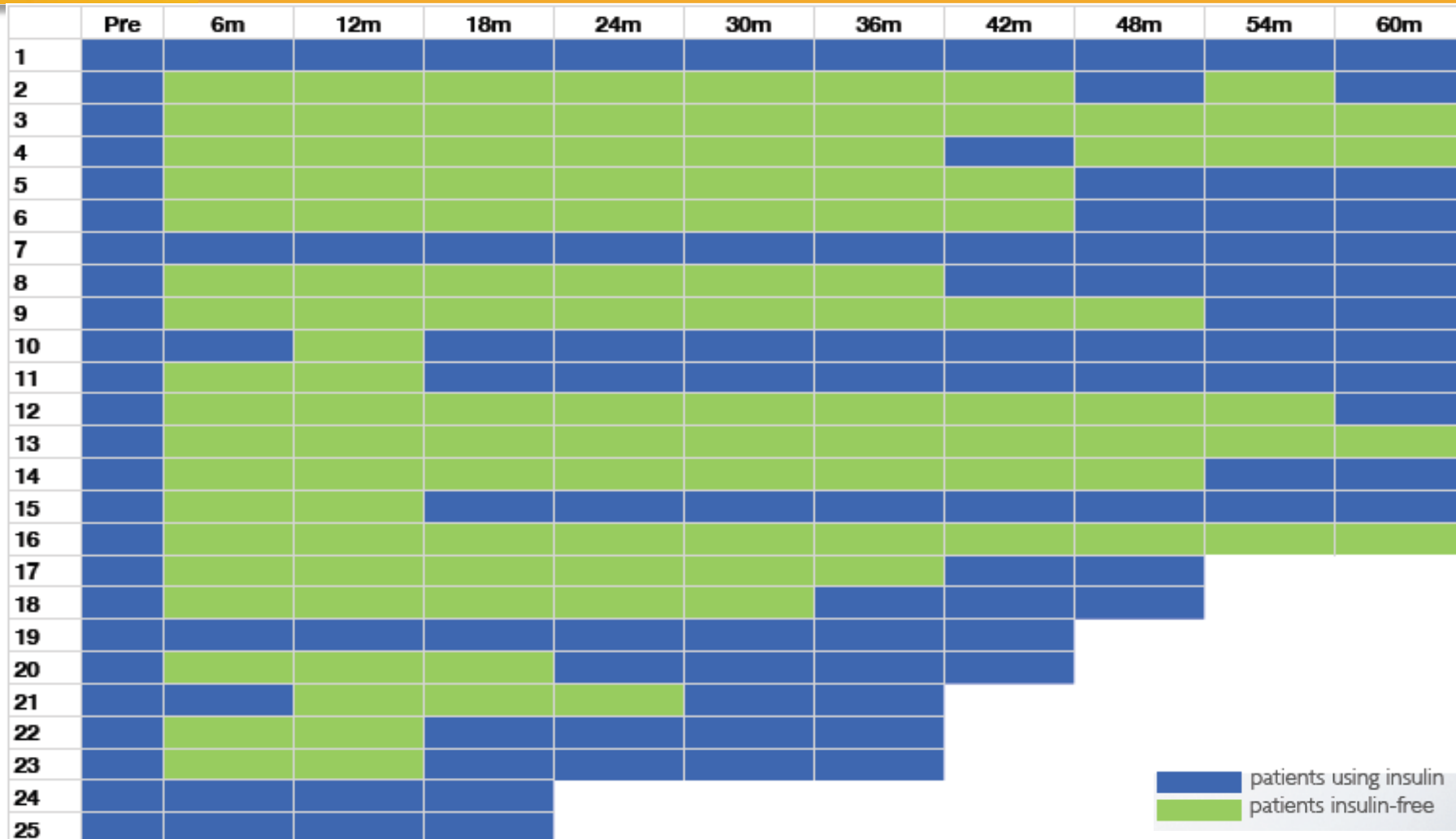
SCT in Diabetes Mellitus type I

| | Pre | 6m | 12m | 18m | 24m | 30m | 36m | 42m | 48m |
|----|---------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 1 | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 2 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin |
| 3 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 4 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin | insulin-free |
| 5 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin |
| 6 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin |
| 7 | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 8 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin | insulin |
| 9 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 10 | insulin | insulin | insulin-free | insulin | insulin | insulin | insulin | insulin | insulin |
| 11 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin | insulin |
| 12 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 13 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 14 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 15 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin | insulin | insulin |
| 16 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free |
| 17 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin | insulin |
| 18 | insulin | insulin-free | insulin-free | insulin-free | insulin-free | insulin-free | insulin | insulin | insulin |
| 19 | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 20 | insulin | insulin-free | insulin-free | insulin-free | insulin | insulin | insulin | insulin | insulin |
| 21 | insulin | insulin | insulin-free | insulin-free | insulin-free | insulin | insulin | insulin | insulin |
| 22 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin | insulin | insulin |
| 23 | insulin | insulin-free | insulin-free | insulin | insulin | insulin | insulin | insulin | insulin |
| 24 | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin |
| 25 | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin | insulin |

insulin patients using insulin
insulin-free patients insulin-free



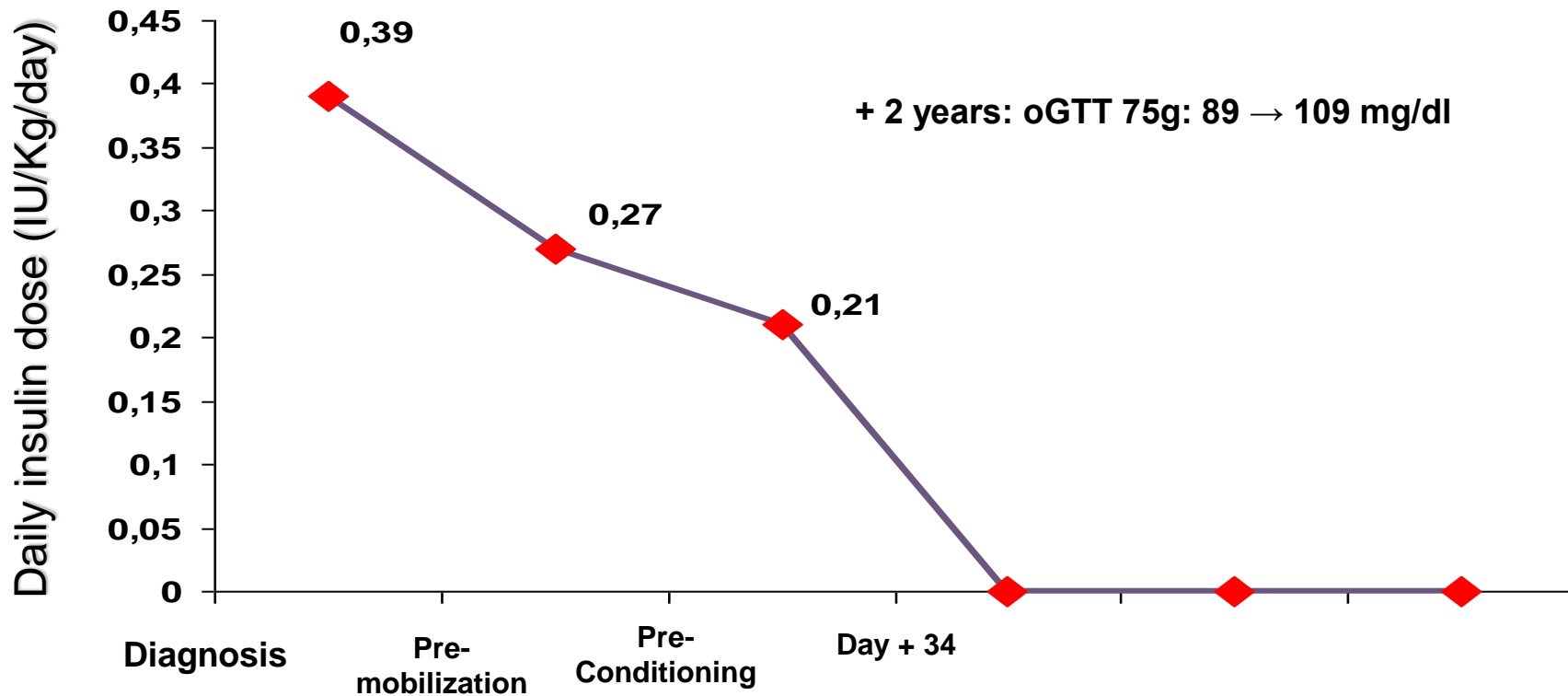
SCT in Diabetes Mellitus type I





Paciente 3 - Masculino 21 anos

SCT in Diabetes Mellitus type I

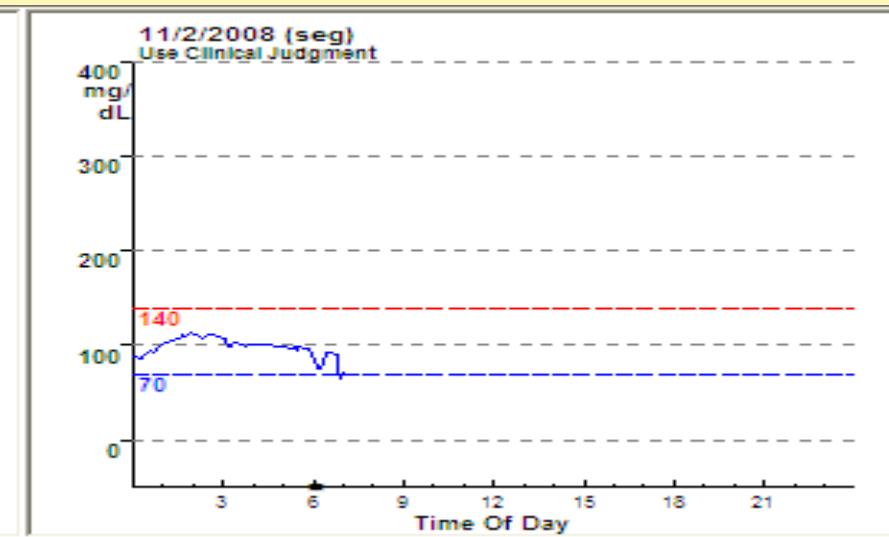
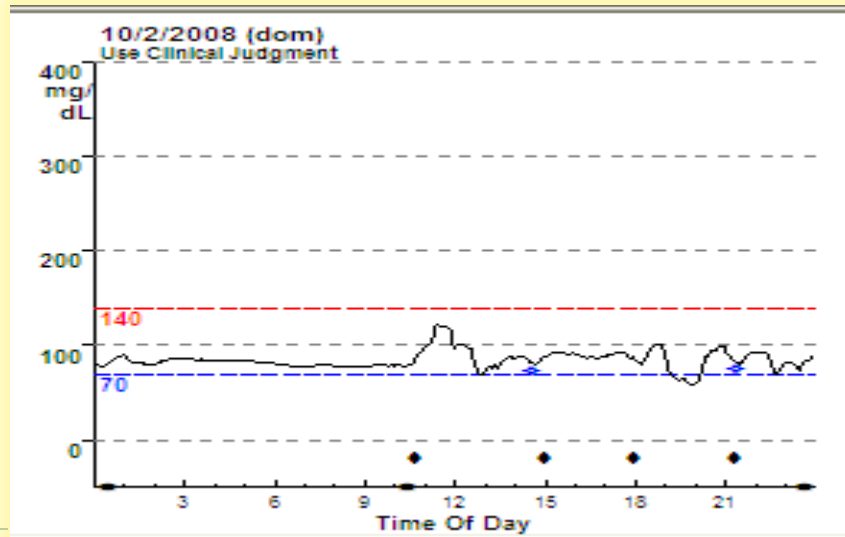
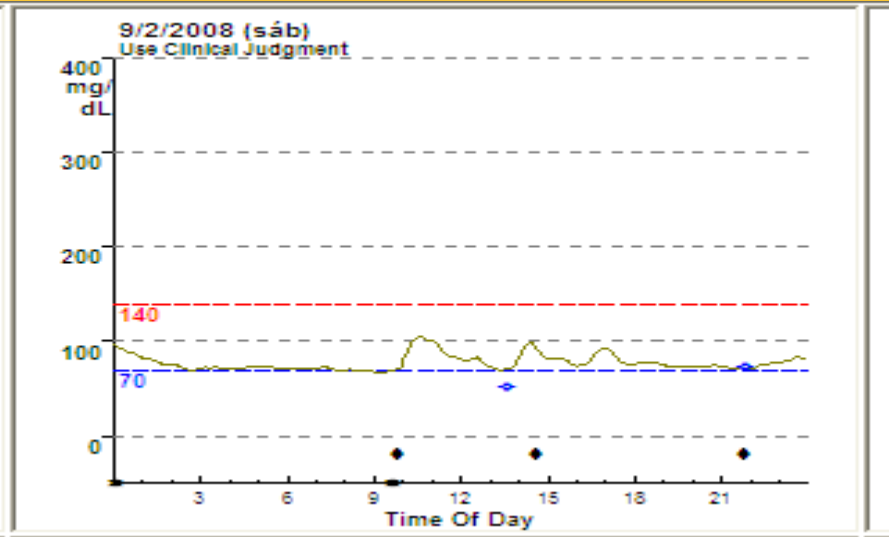
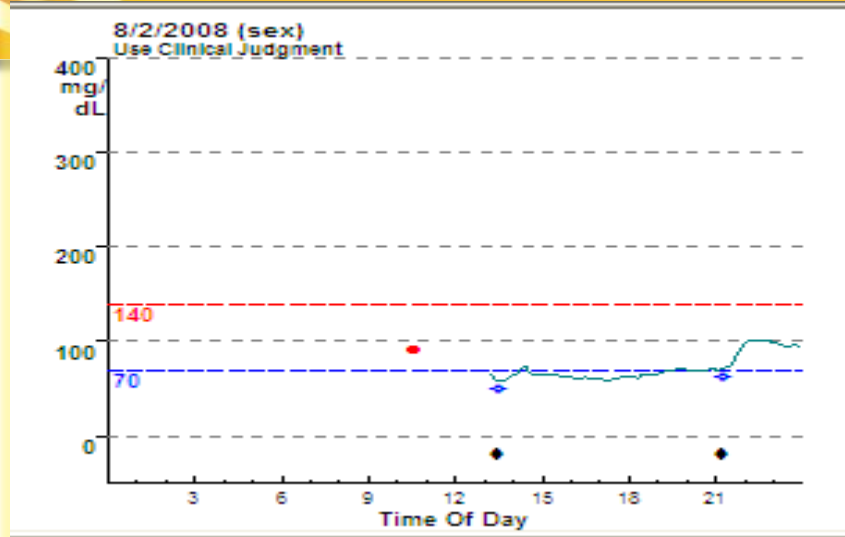


8y 2 m



3-day-Continuous Glucose Monitoring

Paciente 5 - Masculino 21 años





Bone Marrow Transplantation (2011) 46, 562–566
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www.nature.com/bmt

ORIGINAL ARTICLE

Independence of exogenous insulin following immunoablation and stem cell reconstitution in newly diagnosed diabetes type I

E Snarski¹, A M
K Jedynasty², E

¹Department of Hematology,
Internal Diseases, D
Poland and ³Depart

J Clin Endocrinol Metab, May 2012, 97(5):1729–1736

Endocrine Research

Autologous Hematopoietic Stem Cell Transplantation Modulates Immunocompetent Cells and Improves β -Cell Function in Chinese Patients with New Onset of Type 1 Diabetes

Lirong Li,* Shanmei Shen,* Jian Ouyang, Yun Hu, Limin Hu, Weijuan Cui, Ning Zhang, Yu-zheng Zhuge, Bing Chen, Jingyan Xu, and Dalong Zhu

Divisions of Endocrinology and Hematology, the Affiliated Drum Tower Hospital of Nanjing University, Nanjing 210008, China

P Boguradzki¹,

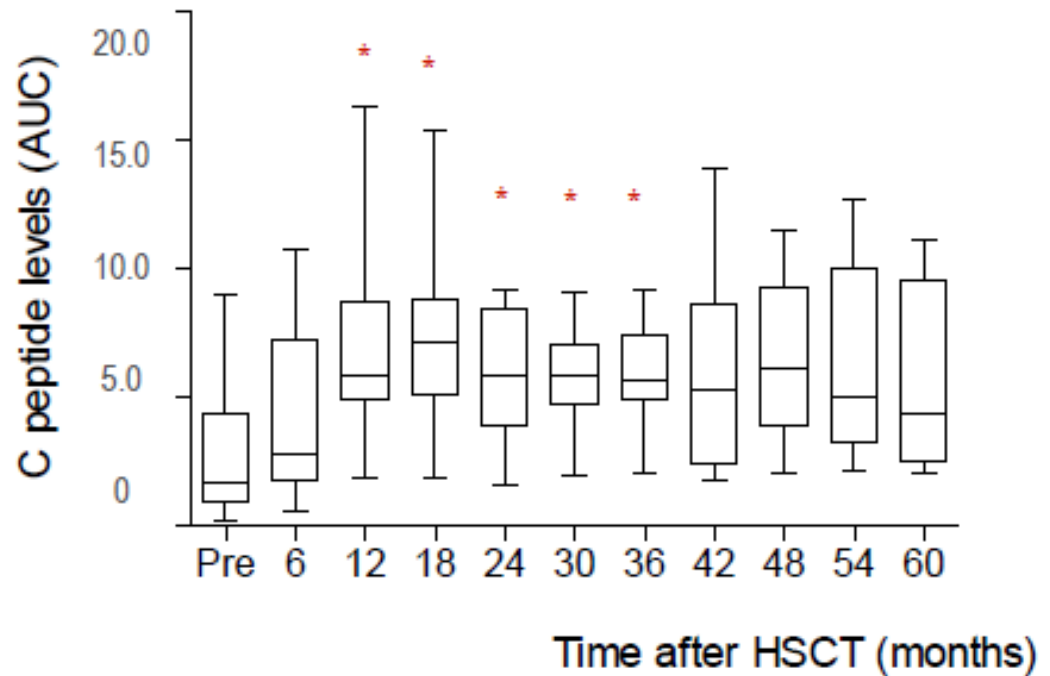
¹Department of Hematology,
Warszawa, Poland
²Department of Hematology,
Warszawa, Poland





SCT in Diabetes Mellitus type I

- ▶ Prognostic factors
 - ▶ Age
 - ▶ C-peptide levels pre-transplant
 - ▶ Time of the year!





- ▶ Prognostic factors
 - ▶ Previous ketoacidosis

Diabetes Care Symposium

ORIGINAL ARTICLE

Diabetic Ketoacidosis at Diagnosis Influences Complete Remission After Treatment With Hematopoietic Stem Cell Transplantation in Adolescents With Type 1 Diabetes

WEIQIONG GU, MD¹
JIONG HU, MD, PHD²
WEIQING WANG, MD¹
LIRONG LI, MD³
WEI TANG, MD²
SHOUYUE SUN, MD¹

WEIJUAN CUI, MD³
LEI YE, MD, PHD¹
YIFEI ZHANG, MD, PHD¹
JIE HONG, MD, PHD¹
DALONG ZHU, MD³
GUANG NING, MD, PHD^{1,4}

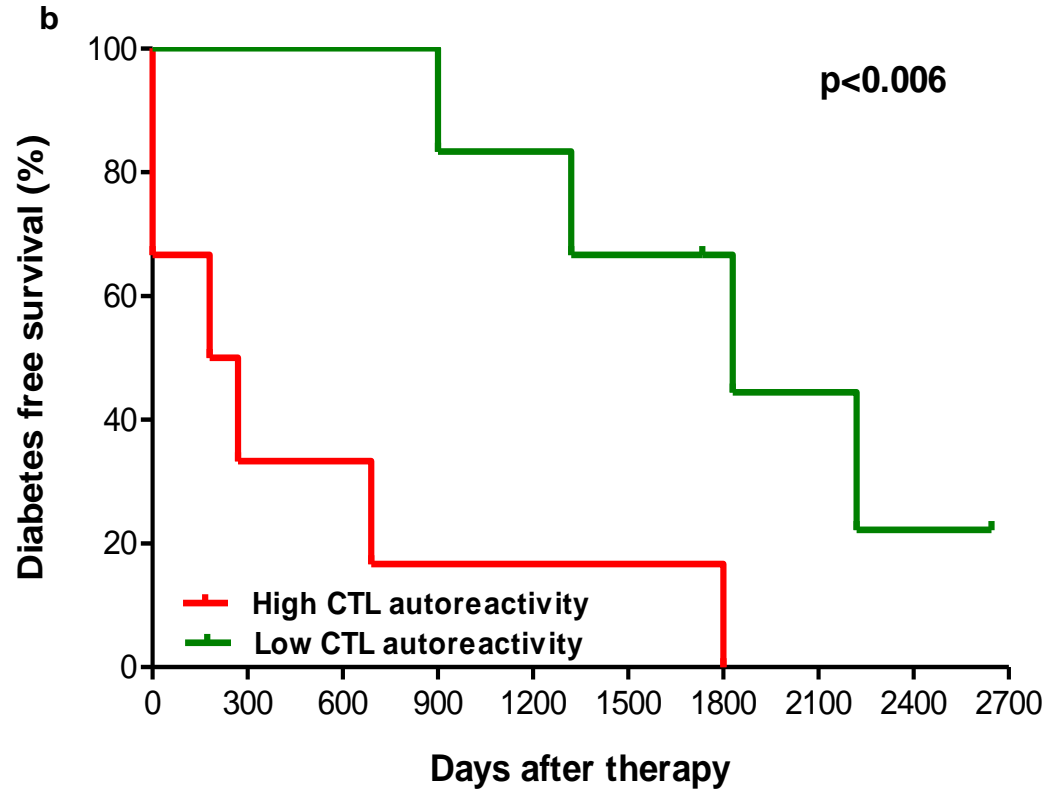
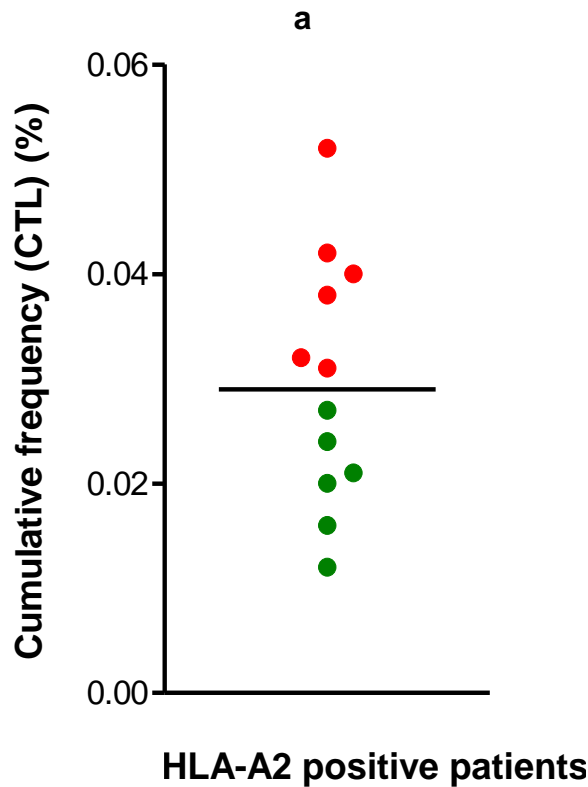
Clinical trials show that autologous nonmyeloablative hematopoietic stem cell transplantation (AH SCT) is an exciting and promising therapy for wide-spectrum diseases, such as autoimmune disorders (1–3) and cardiac and

N=28 pts

% insulin free : (70.6% in non-DKA vs. 27.3% in DKA, $P = 0.051$)



Autoreactivity in DM type I



More or less than 3 years insulin free



Ongoing and Future Programms

▶ MS

- ▶ MISST Trial - randomized international study – SCT vs Natalizumab or Fingolimod
- ▶ Neuromyelitis optica – new protocol

▶ Systemic Sclerosis

- ▶ Randomized study (with and without Rituximab)
- ▶ Retrospective study comparing CD34 selection versus no selection (EBMT)
- ▶ Maintenance after transplant (MMF vs Mesenchymal stem cells) - EBMT

▶ Diabetes type I

▶ MSC

- ▶ 8 adults and 6 children already included – no response
- ▶ AutoSCT with ATG, Cyclophosph, Fludara, ATG (ASTID)
 - ▶ Randomized Study vs best available treatment – continuous insulin infusion)
 - ▶ USA, France, England and Brazil - EBMT

▶ Crohn´s Disease





Daniela
Moraes

George
Navarro

Carolina
Oliveira

Beatriz
Stracieri

Guilherme
Darrigo

Fabiano
Pieroni



**Daniela
Moraes**

**Carolina
Oliveira**

**Carlos Eduardo
B. Couri**



Edson Silva/ Folhapress

Julio Voltarelli





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- Dra. Ana Beatriz de Lima Stracieri

➤ Hematologist

- Dr. Fabiano Pieroni
- Dr. Renato Cunha
- Dra. Juliana Elias
- Dr. Guilherme Darrigo

➤ Neurologist

- Prof. Dr. Amilton Nunes Barreira
- Dra. Doralina Brum

➤ Endocrinologist

- Dr. Eduardo Couri

➤ Radiologist

- Dr. Antonio Carlos dos Santos

➤ Blood Bank and GMP Laboratory

- Dr. Dimas Tadeu Covas
- Dra. Karen de Lima Prata
- Maristela Orelana

➤ SC – Preparation and cryopreservation

- Dr. Gil de Santis
- Dr. Benedito Pina de Almeida Prado

➤ Nurses

- Maria Carolina (Allo SCT Unit)
- Andreia Zombrilli (Autoimmune Unit)

➤ International Cooperation

- Richard Burt (Chicago)
- Marcelo Pasquini (CIBMTR)
- Dominique Farge (EBMT)
- Bart Roep (Holand)



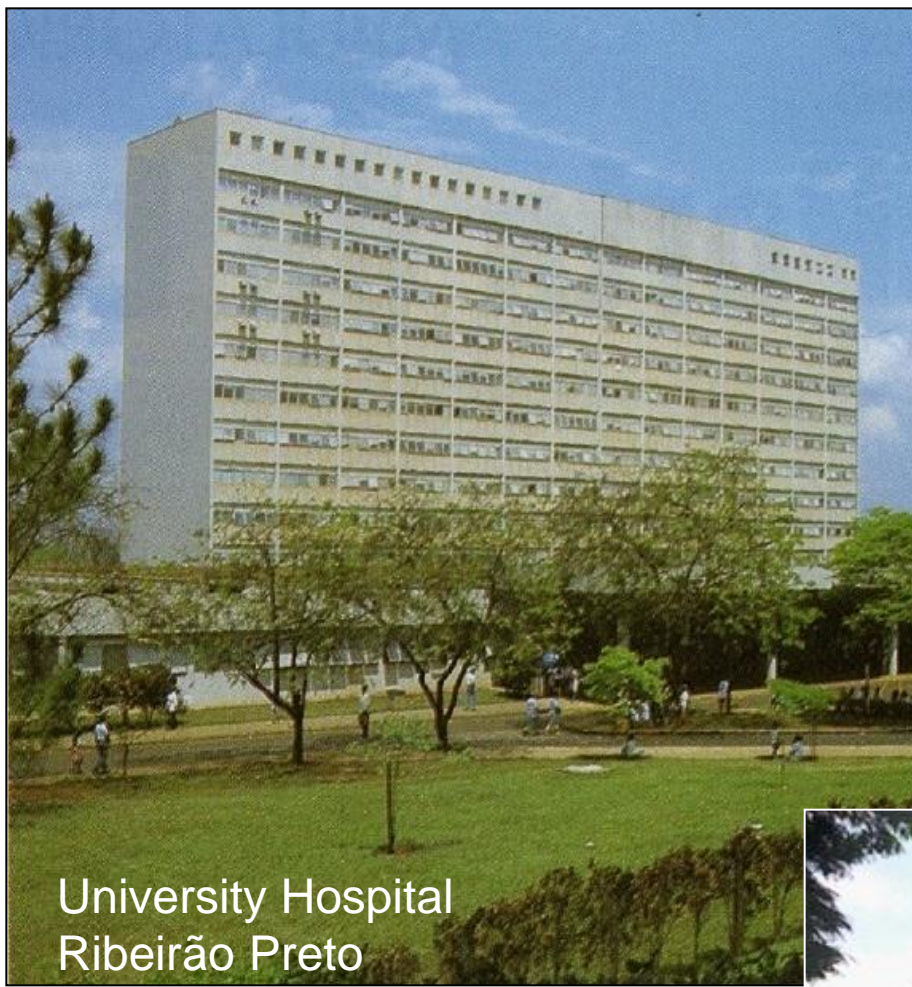


Ribeirão Preto Hospital



Medical School Ribeirão Preto
University of São Paulo





University Hospital
Ribeirão Preto



Blood Bank and GMP-Laboratories



Medical School Ribeirão Preto

