

- ### Insulin analogues: desired properties
- Meal-related analogues (e.g. aspart, lispro) designed to give:
 - Rapid absorption
 - Peak action coinciding with peak carbohydrate absorption
 - Basal insulin analogue should provide:
 - Slow and steady rate of absorption
 - Protracted action
 - Low within-subject variability in action

- ### Insulin lispro
- is rapid-acting and should be given immediately before meals
 - improves post-prandial glucose control compared to human insulin
 - reduces night-time hypoglycemia compared to human insulin
 - improves HbA_{1c} compared to human insulin when used in CSII
- ### Insulin aspart
- is rapid-acting and should be given immediately before meals
 - has a similar effect profile as insulin lispro when injected or used in CSII
 - has, in large studies, shown significant small mean reductions in HbA_{1c} compared to HI
 - improves post-prandial glucose control compared to HI
 - reduces night-time hypoglycaemia compared to HI
- Best Pract Rec Clin Gastroenterol, 2002

Insulin glargine

- is a basal insulin with a long half-life suitable for once-daily administration
- is presented as a clear acidic fluid that crystallizes after injection
- has a very flat pharmacokinetic profile
- reduces night-time hypoglycaemia compared to human NPH insulin

Insulin detemir

- is a basal insulin with a half-life between that of NPH-insulin and insulin glargine
- is presented as a clear neutral fluid that can be mixed with other insulins
- is less variable in pharmacokinetics and glycaemic control compared to NPH-insulin
- reduces night-time hypoglycaemia compared to human insulin

Best Pract Rec Clin Gastroenterol, 2002

Therapeutic potential of intensive analogue-based insulin therapy

Achievement and maintenance of glycaemic targets:

- HbA_{1c}
- Postprandial plasma glucose
- Fasting plasma glucose
- Low within-subject variability
- Reduced risk of hypoglycaemia
- Minimal weight gain
- Enhanced convenience and improved quality of life

Pediatric Diabetes 2005; 6: 130-134
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Pediatric Diabetes

Original Article

Use of insulin glargine in children under age 6 with type 1 diabetes

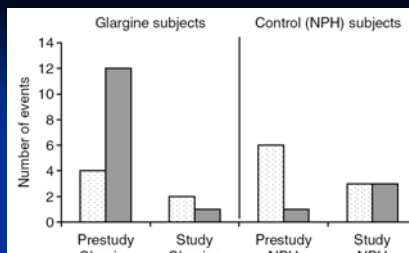


Fig. 1. Incidences of severe hypoglycemia (SH) in the 6 months before glargine (prestudy) and during the 6 months of glargine use (study) are presented for both groups. The open bars represent daytime episodes and shaded bars represent nighttime episodes. NPH, neutral protamine Hagedorn.

Pediatrics Diabetes, 2005

Number of Insulin injections per day in different countries

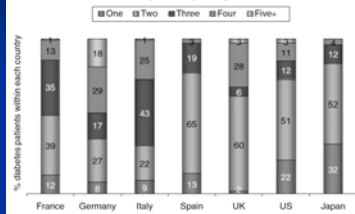


Fig. 1. Injection frequency in per cent of all patients with diabetes in different countries according to a large international telephone survey on market research in 2002 (14).

Pediatrics Diabetes, 2006

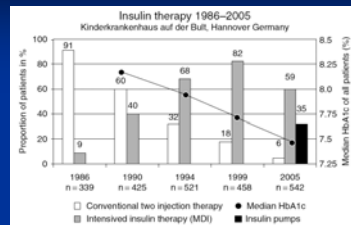


Fig. 2. Change from conventional insulin therapy with a high proportion of patients with premixed insulins to multiple daily injection (MDI) and continuous subcutaneous insulin infusion over the recent years and the respective change of the median HbA_{1c} (line). HbA_{1c}, hemoglobin A_{1c}; MDI, multiple daily injection.

Pediatrics Diabetes, 2006

Table 1. Optimal characteristics for insulin pump candidates

Motivational factors

- Seeking to lower glucose and hemoglobin A1c (HbA1c) levels
- Seeking to reduce risk of hypoglycemia
- Seeking improved lifestyle
- Interested in trying this approach to insulin treatment
- Realistic expectations

Treatment factors

- History of good self-management skills and reliable follow-up
- Ability to perform carbohydrate counting
- Performing four or more blood glucose tests per day
- Adequate control on injection therapy
- Reliable adult supervision
- Able to master technical aspects of pump therapy
- Active communication with the Diabetes Team

Original Article

A cross-sectional international survey of continuous subcutaneous insulin infusion in 377 children and adolescents with type 1 diabetes mellitus from 10 countries

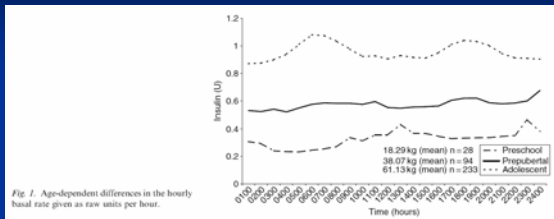


Fig. 1. Age-dependent differences in the hourly basal rate given as raw units per hour.

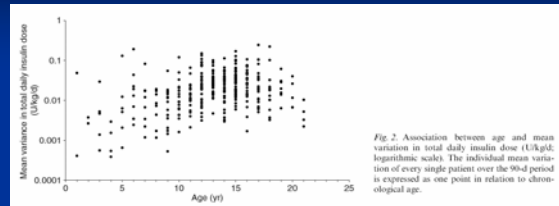


Fig. 2. Association between age and mean variation in total daily insulin dose (U/kg/d, logarithmic scale). The individual mean variation of every single patient over the 90-d period is expressed as one point in relation to chronological age.

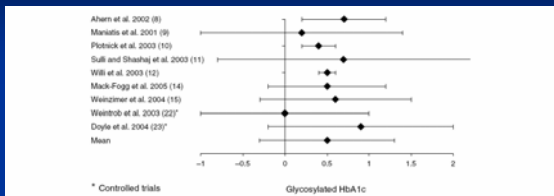


Fig. 3. Reduction in glycosylated hemoglobin A1c (HbA1c) after beginning of continuous subcutaneous insulin infusion (CSII) in pediatric studies.

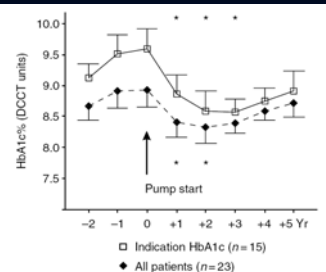


Fig. 4. Long-term follow-up of HbA1c before and after pump start. HbA1c was calculated as a mean of all HbA1c values taken during 1 yr (\pm SE). Dashed line shows the whole pump group ($n = 23$), solid line shows patients with high HbA1c as the indication for pump start ($n = 15$). * $p < 0.05$ vs. year before pump start.

Emerging Treatments and Technologies
ORIGINAL ARTICLE

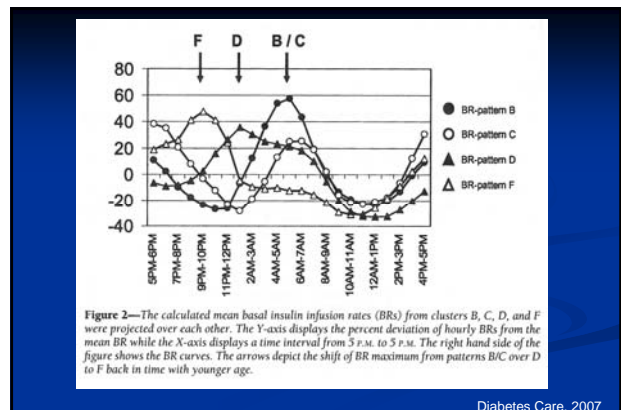
Classification of Distinct Baseline Insulin Infusion Patterns in Children and Adolescents With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion Therapy

PAUL-MARTIN HOLTERBUS, MD¹
RAINER OEDENMIL, MD²
SANDRA OESINGSMANN²
RENKE LEFFER, MD³
VERENA WAGNER, MD²

OLAF HIWERT, MD²
REINHARD HOLL, MD³
THE GERMAN/AUSTRIAN DPV INITIATIVE
AND THE GERMAN PEDIATRIC CSII
WORKING GROUP

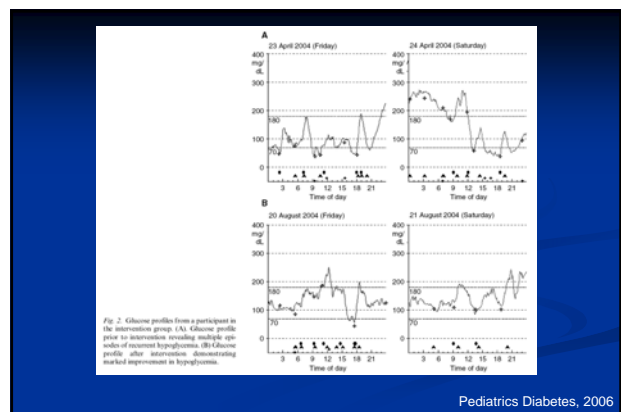
...bution of insulin needs in CSI, which should be kept in mind when considering basal insulin infusion rate strategies in children and adolescents.

Diabetes Care 30:568-573, 2007



Continuous Glucose Monitoring Systems

- > CGMS-Guardian-TGMS* (Medtronic)
- > Glucoday (Menarini)
- > Glucowatch G2 (Cygnus)
- > LTSS-VGMS (Medtronic)*
- > Navigator (Abbot)*
- > DexCom*



Emerging Treatments and Technologies
ORIGINAL ARTICLE

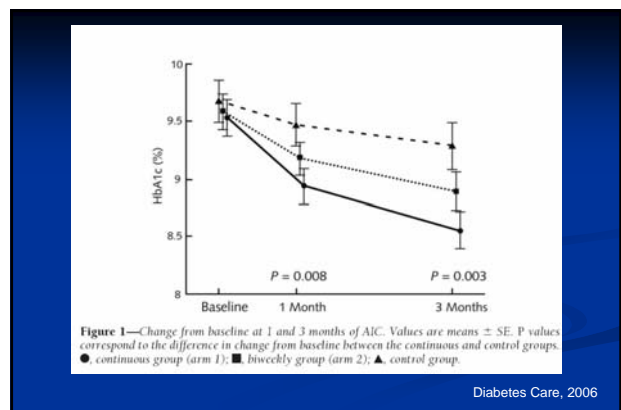
Improved Glycemic Control in Poorly Controlled Patients with Type 1 Diabetes Using Real-Time Continuous Glucose Monitoring

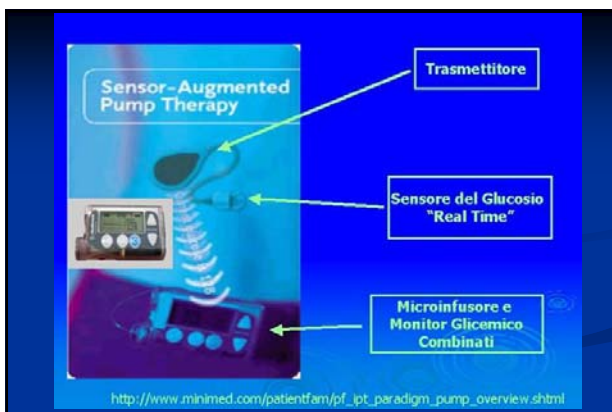
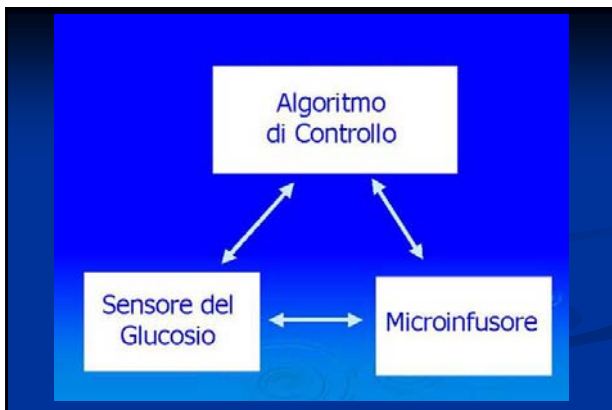
DOROTHEE DISS, MD¹
JON BRUNNER, MD, PhD²
JEAN-PIERRE REYLING, MD³
LUIGI BATTALINO, MD, PhD⁴

EMANUELE BOGLI, MD, PhD⁵
NATHI TIRRELLA-BOI, MD⁶
DAVID KIRK, MD⁷
MOHIB PIRLIZ, MD⁸

...perglycemia with the upper alarm lowering to 200 mg/dl after the first 10 days. Settings could be readjusted during the study.

Diabetes Care, 2006





Paradigm REAL-Time
INSULIN PUMP AND CONTINUOUS GLUCOSE MONITORING SYSTEM

Il trasmettitore

Si collega al sensore ed è posizionato sulla cute per mezzo di un cerotto biadesivo.

Contiene una batteria, l'elettronica necessaria alla trasduzione del segnale glicemico (corrente ISIG), e l'antenna per la trasmissione in radiofrequenza.

Il collegamento del sensore al trasmettitore avvia automaticamente l'inizializzazione del sensore e la comunicazione wireless con Paradigm REAL Time.

È impermeabile (IPX8).





Paradigm REAL-Time
INSULIN PUMP AND CONTINUOUS GLUCOSE MONITORING SYSTEM



Il sensore glicemico viene inserito nel tessuto sottocutaneo, tipicamente nella zona addominale, con l'aiuto di un insertore (SenSeter®).

Il paziente indossa lo stesso sensore per un massimo di 72h durante le normali attività quotidiane (288 letture glicemiche nella giornata).

Per mezzo del trasmettitore wireless collegato al sensore, il valore glicemico rilevato viene inviato ogni 5 minuti a Paradigm REAL Time.

La calibrazione del sistema è idealmente da realizzarsi inserendo 4 glicemie lette da glucometro nell'arco della giornata.

I dati immagazzinati in Paradigm REAL Time possono essere scaricati in un computer per successive analisi



Paradigm REAL-Time
INSULIN PUMP AND CONTINUOUS GLUCOSE MONITORING SYSTEM



Il valore in tempo REALE permette ai pazienti di:

- Scoprire come dieta, esercizio fisico, terapia e stile di vita influenzano la loro glicemia
- Intervenire in tempo REALE per ridurre la frequenza e severità delle ipo ed iperglicemie

REAL-Time

- Valore numerico
- Freccine per il trend
- Grafico delle ultime 3h



Paradigm REAL-Time
INSULIN PUMP AND CONTINUOUS GLUCOSE MONITORING SYSTEM

Analisi storica

- Grafico delle ultime 24h
- Scaricamento e analisi dati via software

Analisi dei dati storici da parte dei medici e dei pazienti:

- Scoprire come dieta, esercizio fisico, terapia e stile di vita influenzano la glicemia del paziente
- Ottimizzazione della terapia
 - Regolazione delle velocità basali
 - Regolazione raffinata delle impostazioni avanzate del microinfusore/calcolatore di boli
 - Adattamento del comportamento del paziente per un migliore controllo metabolico




Paradigm REAL-Time
INSULIN PUMP AND CONTINUOUS GLUCOSE MONITORING SYSTEM

Sistema Paradigm REAL Time : componenti della modalità monitoraggio glicemia



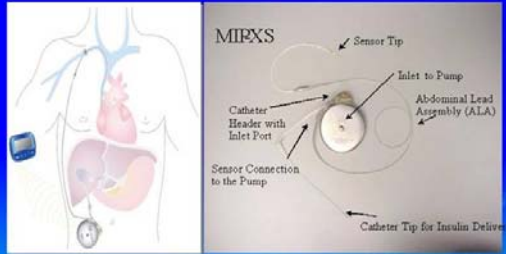

MiniLink REAL-Time
TRANSMITTER

Caratteristiche principali del trasmettitore MiniLink™ REAL-Time

- ✓ È un componente del sistema integrato di microinfusione dell'insulina e monitoraggio continuo della glicemia.
- ✓ Si collega al sensore glicemico, raccoglie i dati della glicemia e li invia al monitor tramite comunicazione mediata da onde radio (wireless).
- ✓ Contiene una batteria ricaricabile e sostituibile ad 8 giorni di un apparato europeo.
- ✓ È fornito di un'apparecchio che indica il corretto modo di usare il bolus.



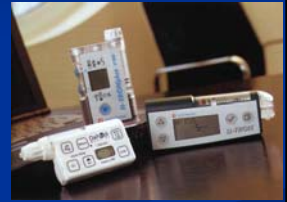

Sistema ad ansa chiusa impiantabile



MICROINFUSORI

Criteri di ordine tecnico

- Caratteristiche di sicurezza, affidabilità e durata
- Semplicità di gestione
- Adeguate caratteristiche tecnologiche
- Dimensioni ridotte e struttura esterna gradevole
- Garanzia da parte dell'azienda produttrice per guasti o necessità di sostituzione.



Commissione Diabetologica-Regione Liguria

CENTRO REGIONALE DIABETOLOGIA PEDIATRICA I. G. GASLINI-GENOVA

Terapia con CSII in 39 pazienti:

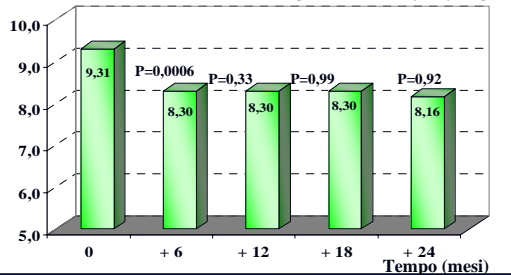
- 28 con DM1 (16 f; 12 m)
- 8 pazienti con DM1 in gravidanza
- 2 DM in FC
- 1 paziente gravida con DM in FC
 - 9 pazienti in stato di gravidanza (nessuna programmata)
 - 28 pazienti avevano un controllo insoddisfacente
 - 2 pazienti presentavano frequenti episodi ipoglicemici

CENTRO REGIONALE DIABETOLOGIA PEDIATRICA I. G. GASLINI-GENOVA

24 pazienti con DM1,
non in stato di gravidanza,
hanno raggiunto un
follow-up di 24 mesi
dall'avvio di CSII

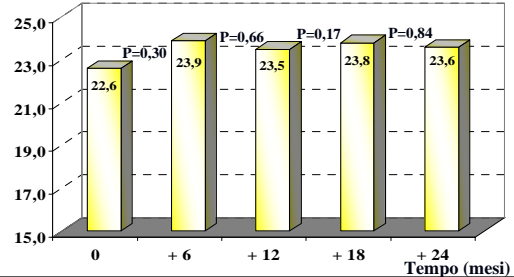
HbA1c (%)

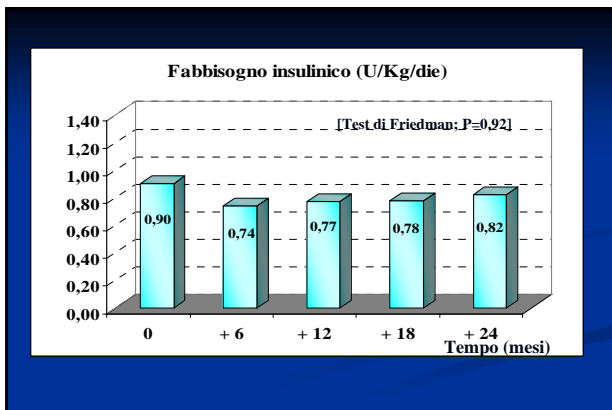
[Test di Friedman; P=0,0005]



BMI (Kg/m²)

[Test di Friedman; P=0,046]





The NEW ENGLAND JOURNAL of MEDICINE

Perspective
FEBRUARY 1, 2007

Finding New Treatments for Diabetes — How Many, How Fast . . . How Good?

David M. Nathan, M.D.

Approved Antidiabetes Medications in the United States.

Medication*	Route of Administration	Year of Introduction or FDA Approval	Efficacy as Monotherapy, Measured as a Reduction in the Glycated Hemoglobin Concentration percentage points
Insulin	Parenteral	1921	≥2.5
Inhaled insulin	Pulmonary	2006	1.5
Sulfonylureas	Oral	1946	1.5
Biguanides	Oral	1957	
Metformin†	Oral	1995	1.5
Alpha-glycosidase inhibitors	Oral	1995	0.5-0.8
Thiazolidinediones	Oral		0.8-1.0
Troglitazone‡	Oral	1997	
Rosiglitazone	Oral	1999	
Pioglitazone	Oral	1999	
Glinides	Oral	1997	1.0-1.5
GLP analogues	Parenteral	2005	0.6
Amylin analogues	Parenteral	2005	0.6
DPP-IV inhibitors	Oral	2006	0.5-0.9

* GLP denotes glucagon-like peptide, and DPP-IV dipeptidyl peptidase IV.
† Metformin has been available in other countries since 1957 but was approved in the United States in 1995.
‡ Troglitazone was approved in 1997 but was withdrawn from the market in 2000 because of hepatotoxicity.

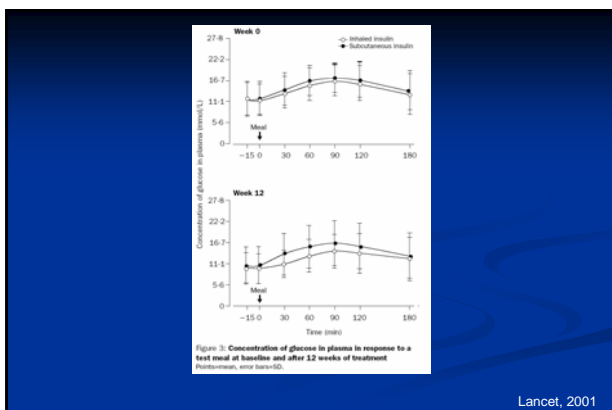
N Engl J Med, 2007

Articles

Efficacy of Inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study

Jay S Skyler, William T Cefalu, Ione A Kourides, William H Landschutz, Cecile C Balagtas, Shu-Lin Cheng, Robert A Goffand for The Inhaled Insulin Phase II Study Group*

Lancet, 2001



The NEW ENGLAND JOURNAL of MEDICINE

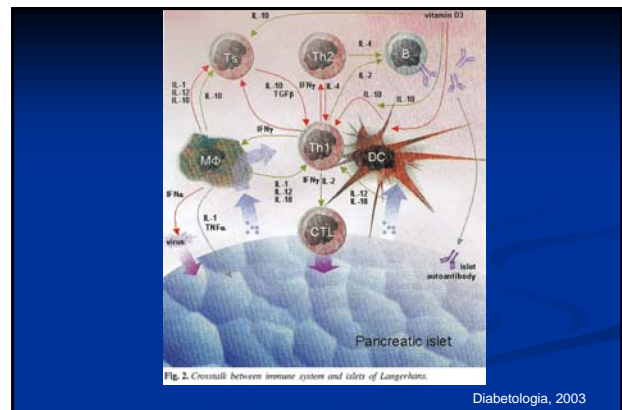
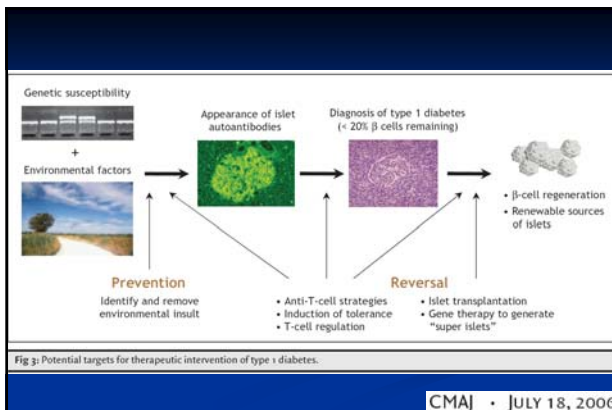
CLINICAL THERAPEUTICS

Inhaled Insulin for Diabetes Mellitus

Graham T. McMahon, M.D., M.M.Sc., and Ronald A. Arky, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

N Engl J Med, 2007

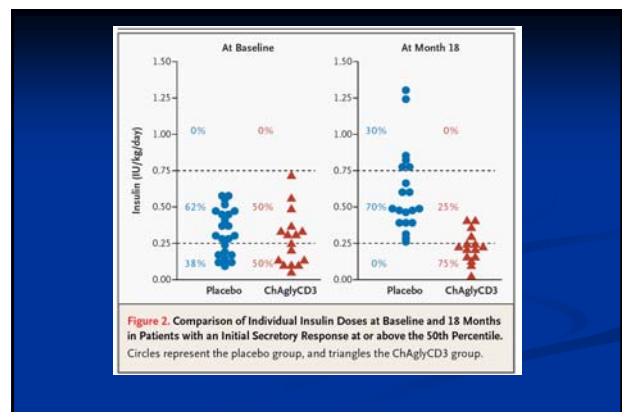


THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes

Bart Keymeulen, M.D., Ph.D., Evy Vandemeulebroecke, M.D., Anette G. Ziegler, M.D., Ph.D., Chantal Mathieu, M.D., Ph.D., Leonard Kaufman, Ph.D., Geoff Hale, Ph.D., Frans Gorus, M.D., Ph.D., Michel Goldman, M.D., Ph.D., Markus Walter, M.D., Sophie Candon, M.D., Ph.D., Liliane Schandene, Ph.D., Laurent Grenier, M.D., Christophe De Block, M.D., Ph.D., Jean-Marie Seigneurin, Ph.D., Pieter De Pauw, Ph.D., Denis Pierard, M.D., Ph.D., Ilse Weets, M.D., Ph.D., Peppy Rebello, B.Sc., Pru Bird, Ph.D., Eleanor Berrie, Ph.D., Mark Frewin, Herman Waldmann, M.D., Ph.D., Jean-François Bach, M.D., Ph.D., Daniel Pipeleers, M.D., Ph.D., and Lucienne Chatenoud, M.D., Ph.D.



- ### ANTICORPI ANTI-CD3 NEL DIABETE MELLITO
- Follow-up per 18 mesi
 - Risposta C-peptide: maggiore nei pazienti trattati
 - Minore fabbisogno insulinico
 - Effetti collaterali:
 - 75% casi sintomi influenzali
 - 75% casi sintomi tipo mononucleosi infettiva (febbre, malessere, mal di gola, linfonodi ingranditi)
 - Rush cutaneo

- ### HEAT SHOCK PROTEIN PEPTIDE
- hsp60: autoantigene implicato nell'autoimmunità
 - DiaPep277: proteina derivata da hsp60
 - Studi sperimentali topo NOD hanno evidenziato:
 - Arresto della distruzione della beta-cellula
 - Produzione di insulina
 - Nell'uomo: Studio su 49 pazienti slavi e ungheresi DM1 di età 4-14 anni, con DM1 neodiagnostico:
 - Iniezione sottocutanea di DiaPep277:
 - Non significativo aumento di C-peptide

Original Article

Induction of Tolerance in Type 1 Diabetes via Both CD4⁺CD25⁺ T Regulatory Cells and T Regulatory Type 1 Cells

Mamela Battaglia,¹ Angela Stablini,¹ Elena Draghici,² Barbara Migliavacca,¹ Silvia Gregori,¹ Ezio Bonifacio,² and Maria-Grazia Roncarolo^{1,2}

Diabetes, 2006

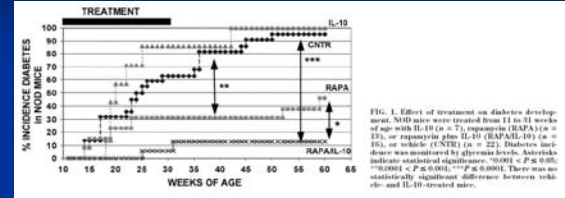


FIG. 1. Effect of treatment on diabetes development. NOD mice were treated from 11 to 31 weeks of age with IL-10 (n = 7), rapamycin (RAPA) (n = 15), or rapamycin plus IL-10 (RAPA+IL-10) (n = 10), or vehicle (CTRL) (n = 22). Diabetes morbidity was monitored by glycemia levels. Asterisks indicate statistical significance: *0.001 < P < 0.05; **0.0001 < P < 0.001; ***P < 0.0001. There was no statistically significant difference between vehicle and IL-10-treated mice.

Diabetes, 2006

Research article

Anti-CD3 and nasal proinsulin combination therapy enhances remission from recent-onset autoimmune diabetes by inducing Tregs

Damien Bressan,¹ Lisa Togher,¹ Evelyn Rodrigo,¹ Yali Chen,² Jeffrey A. Bluestone,³ Kevan C. Herold,² and Matthias von Herrath¹

¹Department of Developmental Immunology, La Jolla Institute for Allergy and Immunology, San Diego, California, USA, ²Roski Barrie Diabetes Center, Division of Endocrinology and Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York, USA, ³Diabetes Center, Department of Medicine, UCSF, San Francisco, California, USA

Safe induction of autoantigen-specific long-term tolerance is the "holy grail" for the treatment of autoimmune diseases. In animal models of type 1 diabetes, oral or i.n. immunization with islet antigens induces Tregs that are capable of bystander suppression. However, such interventions are only effective early in the prediabetic phase. Here, we demonstrate that a novel combination treatment with anti-CD3ε-specific antibody and i.n. proinsulin peptide can reverse recent-onset diabetes in 2 murine diabetes models with much higher efficacy than with monotherapy with anti-CD3ε or antigen alone. In vivo, expansion of CD25⁺Foxp3⁺ and insulin-specific Tregs producing IL-10, TGF-β, and IL-4 was strongly enhanced. These cells could transfer dominant tolerance to immunocompetent recent-onset diabetic recipients and suppressed heterologous autoaggressive CD8 responses. Thus, combining a systemic immune modulator with antigen-specific Treg induction is more efficacious in reversing diabetes. Since Tregs act site-specifically, this strategy should also be expected to reduce the potential for systemic side effects.

J Clin Invest, May 2006

Figure 1: History of Pancreas and Islet Transplantation

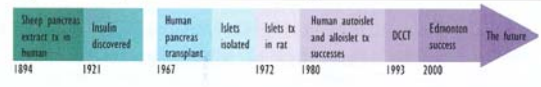
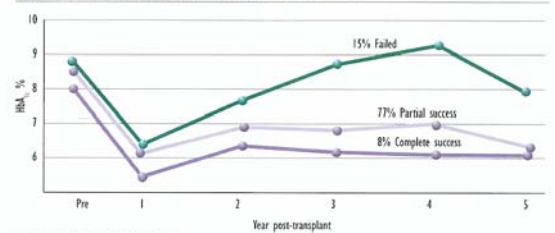
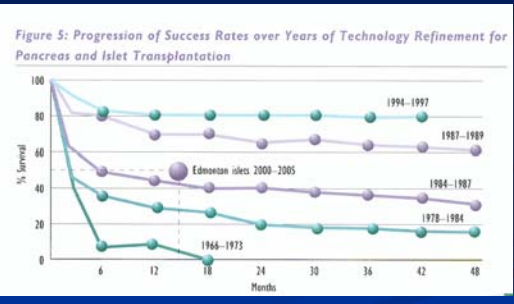


Figure 3: Results from Edmonton Series, 2000–2006



Ryan et al. Diabetes 54:2060, 2005.

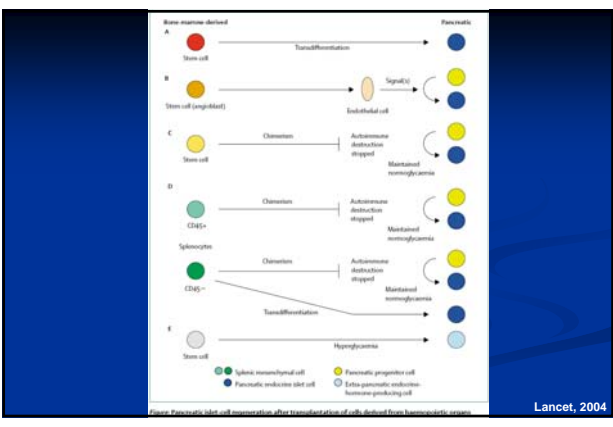


Rapid Review

Stem-cell therapy for diabetes mellitus

Mohib A Hassan, Neil D Theodor

Lancet 2004; 364: 979-85

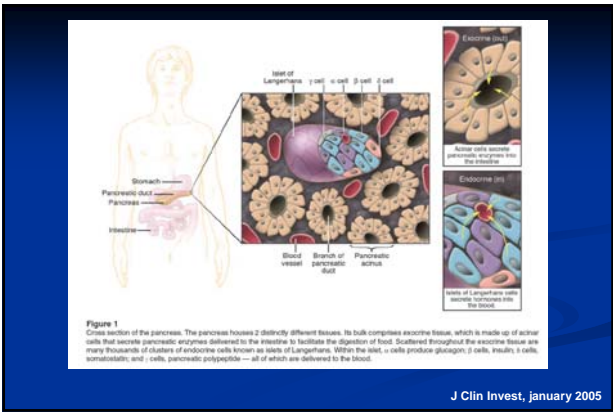


Review

Regeneration of the pancreatic β cell

Massimo Trucco

The Journal of Clinical Investigation | <http://www.jci.org> | Volume 117 | Number 1 | January 2007



ARTICLES

nature
biotechnology

A human β -cell line for transplantation therapy to control type 1 diabetes

Michiki Narushima¹

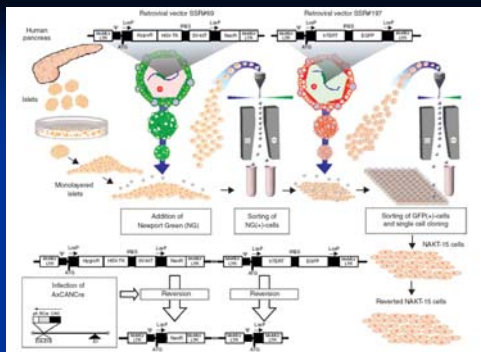
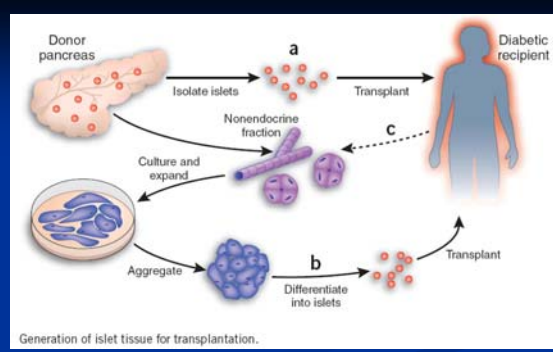


Fig. 1 – Scheme for the establishment of reversibly immortalized human B-cell lines. Freshly isolated human islets were culture in monolayer

Nature Biotech, 2005



Generation of islet tissue for transplantation.

Nature Medicine, 2006

Cell-replacement therapy for diabetes: Generating functional insulin-producing tissue from adult human liver cells

Tamar Sapr^{1*}, Keren Shternhall^{1*}, Irit Melvar-Levy¹, Tamar Blumenfeld^{1*}, Hamutal Cohen^{1*}, Ehud Skutelsky¹

7964-7969 | PNAS | May 31, 2005 | vol. 102 | no. 22

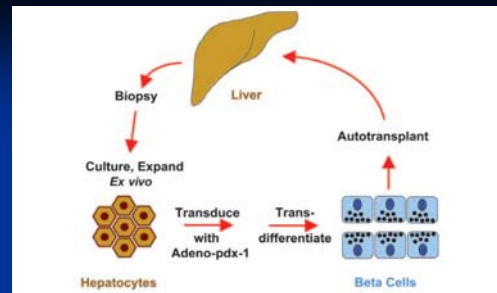


Fig. 1. The hepatocyte-to-beta cell differentiation paradigm. Hepatocytes are obtained by liver biopsy from a donor or patient with diabetes, cultured and expanded ex vivo, transduced with a pdx-1 virus, transdifferentiated into functioning, insulin-producing beta cells, and then transplanted into a patient with diabetes.

PNAS, may 2005

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus

Julia C. Vothawil, MD, PhD
 Carlos E. B. Coust, MD, PhD
 Ana R. F. L. Strazielle, MD, PhD
 Maria C. Oliveira, MD, MS
 Daniela A. Moraes, MD
 Fabiano Pinheiro, MD, PhD
 Marina Cavallini, MD, MS
 Karim C. R. M. de Aguiar, PhD
 Maria C. F. de Freitas, MD, PhD
 Ricardo P. Santos, MD, PhD
 Wilson C. F. de Melo, MD, PhD
 Elizabeth Spass, MD
 Richard K. Burt, MD

Context. Type 1 diabetes mellitus (T1DM) results from a cell-mediated autoimmune attack against pancreatic beta cells. Previous animal and clinical studies suggest that moderate immunosuppression in newly diagnosed type 1 DM can prevent further loss of insulin production and can reduce insulin needs.

Objective. To determine the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (ASCT) in newly diagnosed type 1 DM.

Design, Setting, and Participants. A prospective phase 1/2a study of 15 patients with type 1 DM (aged 14–31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and confirmed with positive antibodies against glutamic acid decarboxylase. Enrollment was November 2003–July 2006 with observation until February 2007 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil. Patients with previous diabetic ketoacidosis were excluded after the first patient with diabetic ketoacidosis failed to benefit from ASCT. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m²) and granulocyte colony-stimulating factor (10 ng/kg per day) and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were injected intravenously after conditioning

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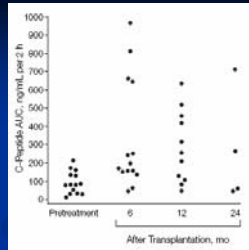
Table 2. Pretreatment and Follow-up Variables of Type 1 Diabetic Patients Undergoing Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation (Anti-Glutamic Acid Decarboxylase, C-Peptide, Insulin Dose, Insulin-Discontinuation Time, Insulin-Free Time)

Patient No.	Diag. (mo)	Anti-Glutamic Acid Decarboxylase, UPE/L ¹				C-Peptide (Fasting) ² Peak Stimulated, ng/mL ¹				Insulin Dose, U/kg per Day ³				Time Free From Insulin, mo ⁴	
		6 mo	12 mo	24 mo	36 mo	Pre-treatment	6 mo	12 mo	24 mo	36 mo	Pre-treatment	Pre-treatment to 24 mo	24 mo to 36 mo		36 mo to 48 mo
1	36.0	9.9	7.7			0.8NA	0.4/0.4	0.5/0.4			0.48	0.31	0.79	NA	0
2	48.0	19.0	20.0	17.0	23	0.3/0.6	0.3/0.7	0.5/1.2	0.5/1.1	2.0/4.6	0.29	0.34	0.30	+48	35
3	1.1	0.0	0.0	0.0	8	0.3/1.0	0.9/1.6	1.6/2.2	1.7/1.8	0.39	0.27	0.21	+34	30	
4	20.0	20.0	20.0	17.0		1.0/2.8	1.3/2.4	1.8/2.2	2.2/2.9	0.36	0.23	0.18	+2	31	
5	81.0	31.0	24.0	41		0.6/1.1	2.1/2.3	0.3/0.5	2.4/4.4	0.52	0.38	0.27	+1	28	
6	17.0	4.6	1.6			0.3/1.8	2.1/2.0	0.6/1.5		0.26	0.42	0.42	-8	25	
7	4.0	14.0	8.0			0.08/0.09	0.3/2.6	1.6/2.3		0.48	0.44	0.17	+610	1	
8	48.0	9.5	6.4			0.3/0.4	0.7/2.0	1.3/4.8		0.29	0.35	0.34	0	17	
9	102.0	31.0	30.0			0.08/0.4	0.6/2.5	1.1/3.9		0.42	0.35	0.39	-1	17	
10	44.0	16.0	13.0			0.4/1.2	0.3/1.7	0.3/3.5		0.61	0.29	0.25	-2	5	
11	11.0	4.4	6.5			0.9/0.4	0.3/1.7	0.8/0.7		0.10	0.13	0.20	-3	12	
12	11.0	10.0				0.06/0.3	2.0/7.9			0.22	0.45	0.36	0	9	
13	24.0	21				0.5/3.1	0.5/2.9			0.28	0.38	0.28	-2	8	
14	37.0	29				0.1/1.6	3.0/2.2			0.32	0.37	0.05	-3	7	
15	21.1					0.5/0.8				0.46	0.44	0.67	-1	6	
Mean ⁵	31.8	17.3	12.5	18.7		0.4/1.9	1.1/4.0	1.0/3.7	1.9/4.5	0.36	0.30	0.32	1.7	14.8	
SD ⁶	27.5	13.2	8.9	19.8		0.3/1.9	0.9/3.7	0.5/3.0	1.1/3.7	0.14	0.13	0.23	103 ⁷	11.3	

Abbreviations: NA, not available.
¹Concomitant factor treatment (c-peptide to insulin, ng/mL) by 0.32/1.
²Insulin and/or oral antidiabetic agent (insulin and/or antidiabetic agent) by 0.22 between pretreatment and 6 mo; P = .12 between pretreatment and 6 mo; P = .11 between 6 and 12 mo; P = .48 between 12 and 24 mo.
³Values related to stem-cell infusion.
⁴Only patients who were followed up for more than 1 year are included.
⁵The patient had transient insulin discontinuation from 2 days prior until 7 days following stem cell infusion and insulin was discontinued again after 1.5 year (see Results).
⁶The patient was lost from retrospective review from 2 days prior until 300 days following stem cell infusion and then resumed insulin use on the day of 0.3 U/kg per day (see Results).
⁷Insulin-free patient 7.

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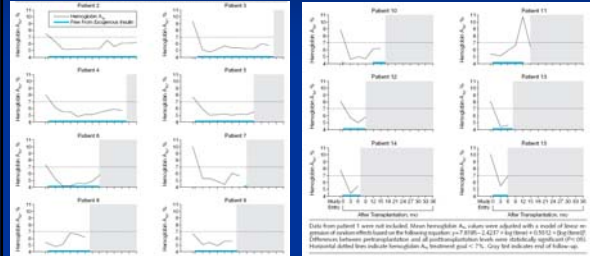
Time Course of Total Area Under the Curve of C-Peptide Levels During Mixed-Meal Tolerance Test



Data from patient 1 were not included. Statistical analysis was performed using a model of multiple regression of mixed effects. $P < .001$ between pretransplant and 6 months; $P = .85$ between 6 and 12 months; $P = .18$ between 12 and 24 months following transplantation. SI conversion factor: to convert C-peptide to nmol/L, multiply by 0.331.

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Hemoglobin A_{1c} Levels and Periods Free From Exogenous Insulin Requirement



Data from patient 1 were not included. Mean hemoglobin A_{1c} values were adjusted with a model of linear regression of posttransplantation hemoglobin A_{1c} for following equation: $y = 0.006x - 0.0277$, where x is time in days. The shaded difference between pretransplantation and all posttransplantation levels were statistically significant ($P < .05$). Horizontal dotted line indicates hemoglobin A_{1c} level of goal < 7%. Gray bar indicates end of follow-up.

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