LDL-aferesi ed aferesi selettiva

Claudia Stefanutti

2007 International Apheresis Registry

Paul S. Malchesky*, Anna P. Koo†, Christine Skibinski†, Angela T. Hadsell*, Lisa A. Rybicki†

International Center for Artificial Organs and Transplantation

INTERNATIONAL SOCIETY FOR APHERESIS ISFA

Cleveland Clinic

20 Centers on 5 continents
1,735 patients with 6,787 treatments

Top Treatment Diagnoses by the Number of Treatments (6,141)

Rank	Asia	Europe	Australia	N America	C/S America	Total
1	Myasthenia gravis (605)	Hypercholest-erolemia (516)	Myasthenia gravis (228)	Chronic relapsing polyneuropathy (88)	Guillain-Barré (5)	**Myasthenia gravis (1,235)**
2	Guillain-Barré (226)	Myasthenia gravis (320)	Chronic relapsing polyneuropathy (86)	Myasthenia gravis (79)	Behcet's disease (3)	**Hyperchol-esterolemia (516)**
3	TTP (224)	Other Circulatory system disease (223)	TTP (65)	Other GI system disease (49)	Myasthenia gravis (3)	**TTP (425)**
4	Other diseases of blood/blood forming organs (220)	HUS (180)	RPGN (20)	non-Hodgkin lymphoma (43)	TTP (3)	**Guillain-Barré (335)**

National View of Therapeutic Apheresis

	Reporting Year	Population Million	Cases	Procedures	Diseases by Frequency	Diseases by #
Canada	2002	30	898	8,561	Hematological, Neurological, Vascular/Renal	TTP, HUS, Myasthenia Gravis, Macroglobulinemias
France	2003 / 04	60	942 / 1,021	9,837 / 10,700	Hematological, Neurological	TTP, HUS, Familial Hypercholesterolemia
Germany	2002	82	--	6,941	Guillain-Barré, Cryoglobulinemia, MG, SLE, TTP	Myasthenia Gravis Guillain-Barré
Hungary	2001-2004	10	792,-983	2,544,-3,120	Gammopathies, TTP, HUS	Fam. Hyperchol., SLE, Cryo, Guillain-Barré, MG
Italy	2000/ 1994-2004	58	2,820/ 1,477	**15,202/ 15,285**	Guillain-Barré, Cryo, MG, SLE, TTP	**Fam. Hyperchol.,**SLE, Cryo, Guillain-Barré, MG
Japan	1995 2002	127	--	**11,697**	Fam. Hyperchol., Guillain-Barré, Hepatic failure	Fam. Hyperchol., Ulcerative Colitis, Malig. RA, Fulm. Hepatitis
Korea	2003-2006	48	1,182	5,921	Hematological, Metabolic, Neurological	ABO Incompatibility, TTP, MG, Hyperviscosity, Hepatic Failure
Philippines	1994-2004	73-83	194	735	Neurological, Hematological, Renal/Metabolic/ Immunologic	Polyradiculoneuropathy, MG, TTP
USA	1991	252	--	**48,221**	Guillain-Barré, Leukemia, T-cell Lymphoma	--
Venezuela	2003	26	--	547	--	--

Therapeutic Apheresis and Dialysis
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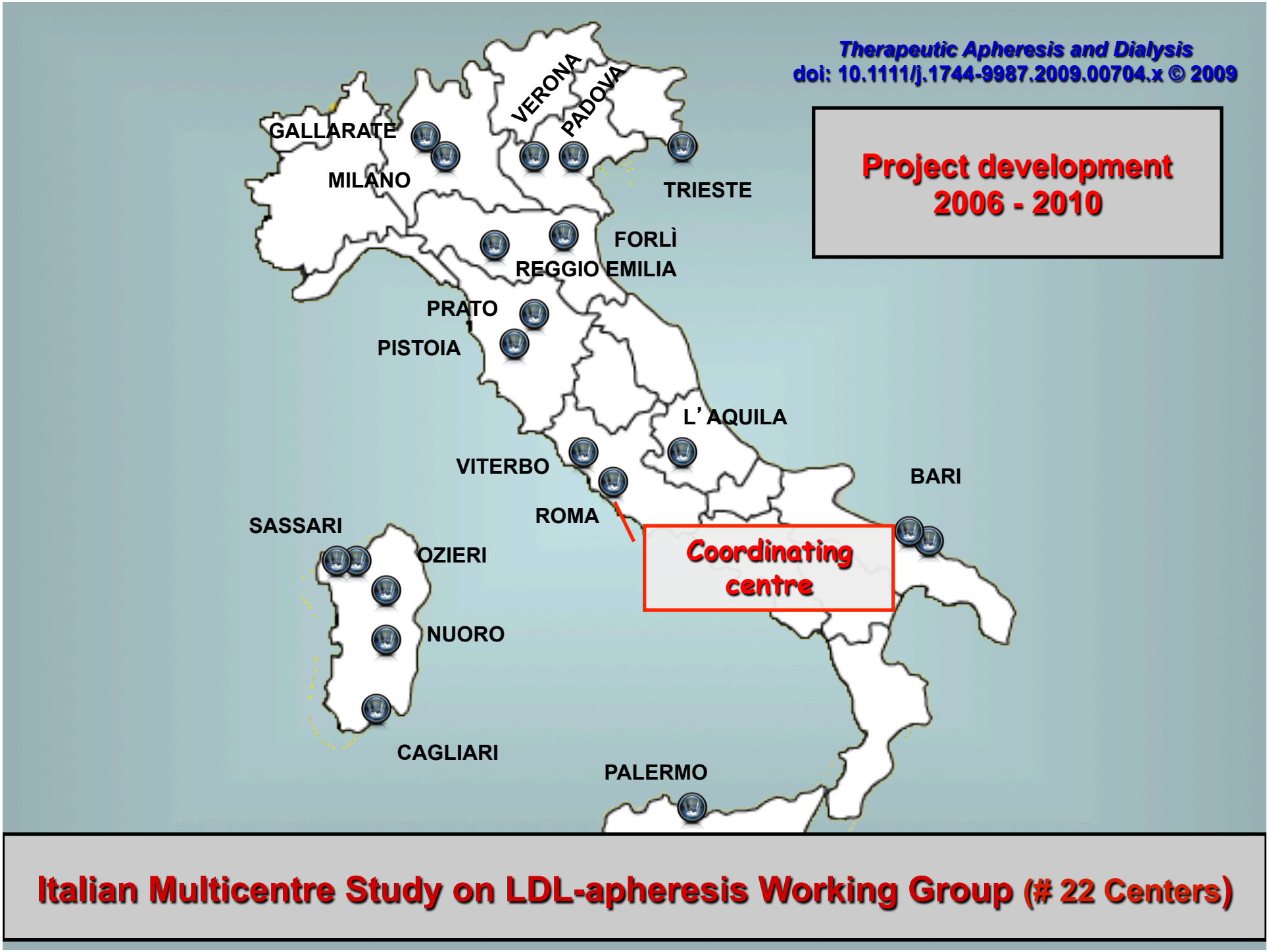

Italian Multicentre Study on LDL-apheresis Working Group (# 22 Centers)

II Consensus Conference Italiana sulla LDL-aferesi *(Italiano)*

Siti Web:

S.I.S.A.
S.I.d. EM.
S.I.N.
A.N.I.F.

Registro Gruppo di Studio Aferesi Terapeutica S.I.N.
Studio Multicentrico Italiano LDL-aferesi (SMILDLa)
Italian Multicenter Study on LDL-apheresis Working Group

The 2009 2nd Italian Consensus Conference on LDL-apheresis

By Claudia Stefanutti ***(Inglese)***

Nutrition, Metabolism & Cardiovascular Diseases
2010 **DOI:10.1016/numecd.2010.04.007**

NMCD Nutrition, Metabolism & Cardiovascular Diseases

he document in extenso online at: http://ees. elsevier.com/nmcd/

Synopsis of Current LDL-Apheresis Technologies

by courtesy of Thomas Bosch

Method	capacity	selectivity	complexity	advantages	disadvantages
Plasma treatment					
DF	++	+(+)	++	hemorheology	loss of IgM
IA	+++	+++	+++	cost-effective	re-use!
DSC	+++	++	++	capacity	bradykinin
HELP	++	++	+++	hemorheology	complexity
Whole blood treatment					
DALI	++(+)	++	+	easy, rapid	bradykinin
DSC-D	++	++	+(+)	easy, rapid	bradykinin

% Reduction of LDL-C, HDL-C, Factor V, VII, VIII

Procedure	Volume treated	LDL-C (%)	HDL-C (%)	Factor V (%)	Factor VII (%)	Factor VIII (%)
IMA	6,2 l	-(60-84%)	-(14-22%)	- 28%	- 28%	- 72%
DSA	4,9 l	-(57-84%)	-(8-11%)	- 74%	- 30%	- 99%
HELP	3 l	-(59-67%)	-(5-17%)	- 63%	- 36%	- 57%
DALI	6,8-9,4 l*	- 77%	-13%	- 68%	- 4 %	- 60%
Lipocollect 200 §	5,5 l	-(64-71%)	-26%	-71%	-18%	-71%

* whole blood while the others means serum

§ *Stefanutti C.et al.* (2009):LDL-apheresis: a novel technique (LIPOCOLLECT 200 ®) *Artif Organs. 33(12):1103–1108.*

Clinical Science (2001) **100**, 191–198 (Printed in Great Britain)

Acute and long-term effects of low-density lipoprotein (LDL)-apheresis on oxidative damage to LDL and reducing capacity of erythrocytes in patients with severe familial hypercholesterolaemia

C. STEFANUTTI*, S. DI GIACOMO*, A. VIVENZIO*, G. C. ISACCHI†, R. MASELLA‡, P. CAPRARI§, R. VARI ‡, A. TARZIA§, A. MOSIELLO‡ and A. CANTAFORA‡

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Effetti della LDL-aferesi sulle chemochine: prospettive di ricerca

Chemochine ed LDL-aferesi Esperimento 1

IL-4	IL-6	IL-10	IL-12 p40 IL-12 p70	TNFR TNFalpha	VEGFR VEGF	IL-1r IL-1 α	SSEL PSEL

Chemochine ed LDL-aferesi Esperimento 2

MCP-1	MIP-1alpha MIP-1beta	G-CSF GM-CSF	IL-1α IL-1β	RANTES	IL-2	IL-6	IFN-γ

Stefanutti C at al, unpublished, 2010

UMBERTO I
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Italian Multicenter Study on Low-Density Lipoprotein Apheresis: Retrospective Analysis (2007)

Claudia Stefanutti and the Italian Multicenter Study on Low-Density Lipoprotein Apheresis Working Group*

Plasmapheresis Unit, Department of Clinical and Medical Therapy, University of Rome "La Sapienza", Umberto I Hospital, Rome, Italy

Therapeutic Apheresis and Dialysis 14(1):79–86
doi: 10.1111/j.1744-9987.2009.00704.x

IMS-LDLa Centers # 18	Year of beginning	# Total sessions	Patients mean age	Range (age)
L'Aquila	2006	66	54	-
Bari 1	2001	638	48	37-62
Bari 2	2006	75	9.5	3-16
Cagliari	1986	6389	41	11-65
Milano	1985	1500	43	15-71
Nuoro	1990	700	40	36-44
Pad				
Pale				
Pist				
Prato	2006	15	56	-
Reggio E.	1990	1480	50	25-73
Ro				
Sas				
Sas				
Sas				
Trieste	1990	1667	62	41-77
Varese	1989	659	69	57-80
Verona	1995	846	58	49-67

IMS-LDLa Center	Year of beginning	# Total sessions	Patient's age/sex
Viterbo	2008	55	65 (1 male)

total procedures: 31012

age (X ± SD): 45.9±14.5

The Italian Multicenter Study on LDL-apheresis (IMS-LDLa): retrospective analysis (2007)

Stefanutti C and the Italian Multicenter Study LDL-apheresis Working Group *

Table 2 IMS-LDLa: devices, mean plasma and blood volumes treated and vascular accesses

IMS-LDLa	P-Ex	CF	DSC	H.E.L.P.	Therasorb	D.A.LI	Lipocollect
# devices	6	4	20	14	4	16	1
MTPV ml	3916.5						
MTBV ml	8735.1						
Vascular accesses	Venous accesses: 84.4 %				AV Fistula: 15.5 %		

MPPV: Mean Treated Plasma Volume
MTBV: Mean Treated Blood Volume

The Italian Multicenter Study on LDL-apheresis (IMS-LDLa): retrospective analysis (2007)

Stefanutti C and the Italian Multicenter Study LDL-apheresis Working Group *

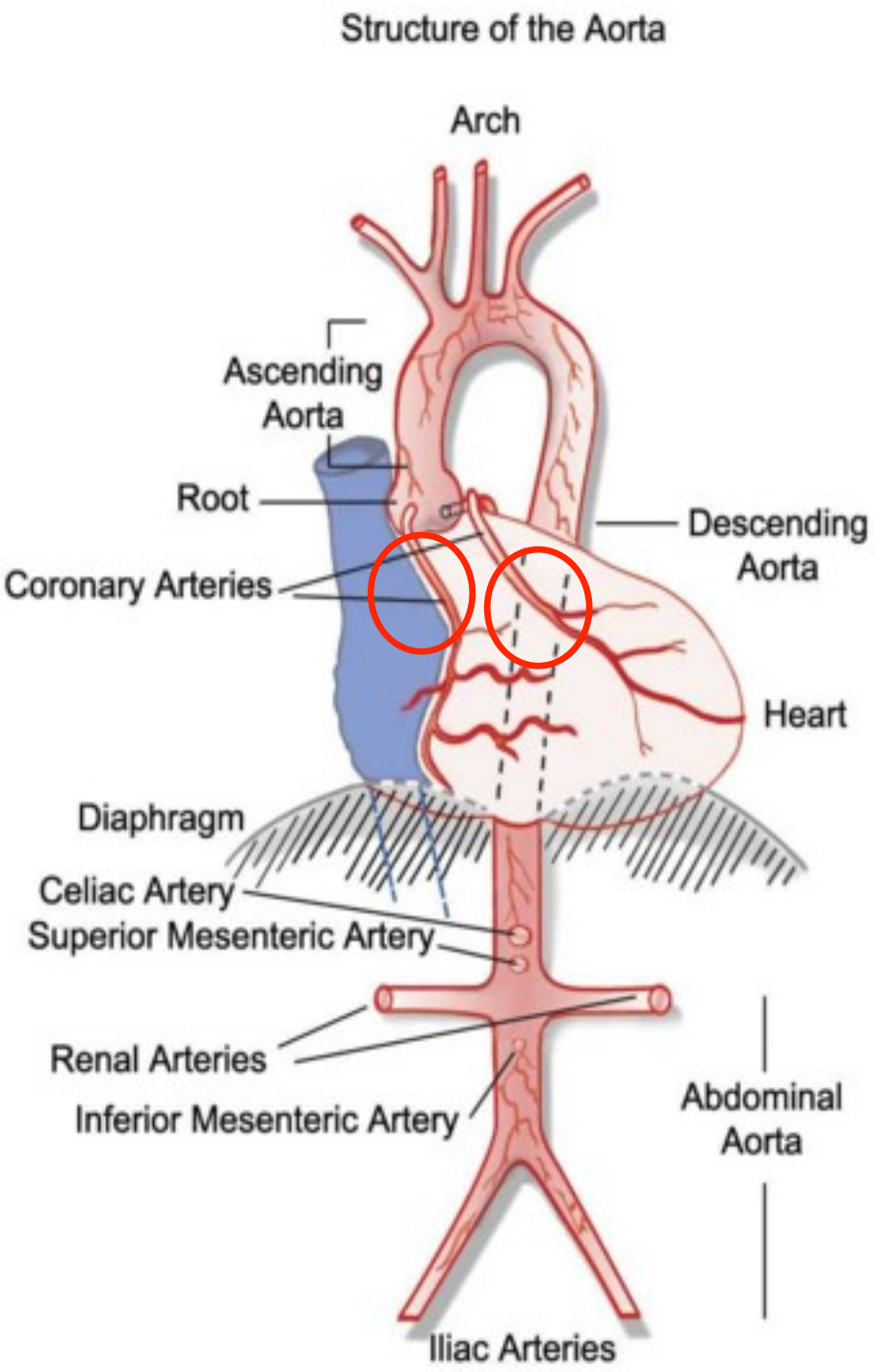
Table 3 IMS-LDLa: # patients selected for hyperlipidemia and treated by LDLa and LA at beginning and actually

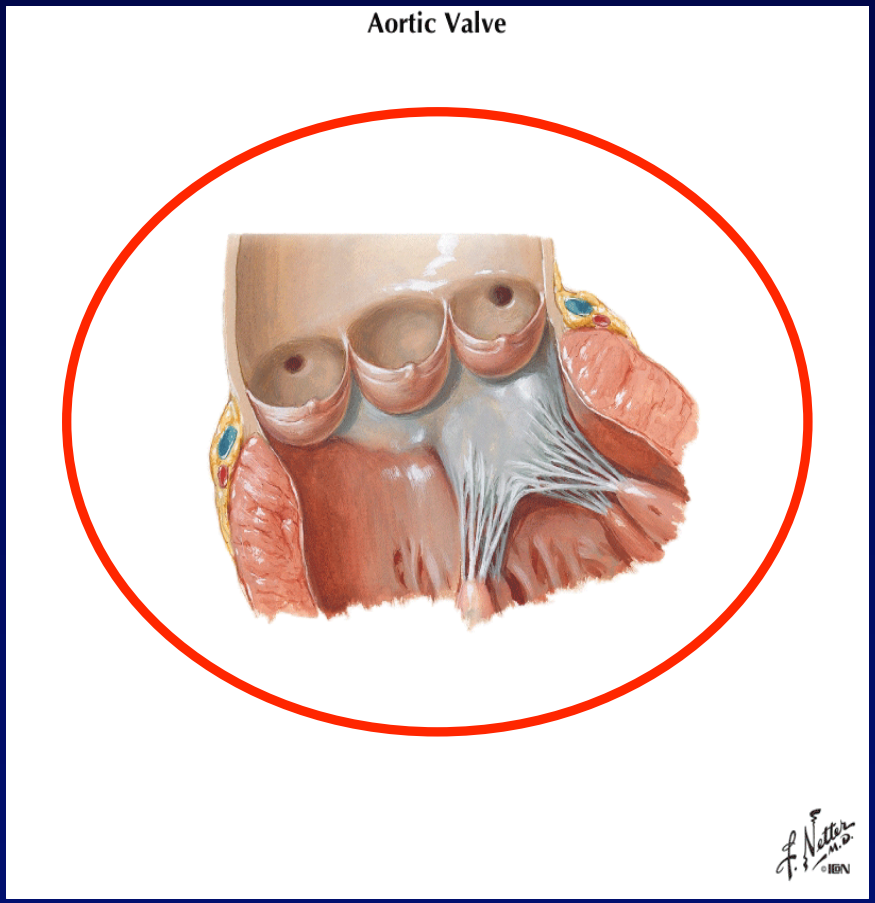
IMS-LDLa Centers	HozFH	DhFH	HetzFH	HyperLp(a)	HyperTG
# of patients at beginning	42	40	110	17	20
current # of patients	27	18	61	12	2
Δ	-15	-22	-49	-5	-18
Total # patients treated from beginning until 2007: 229					
surviving still treated		surviving untreated		Deceased	
120		95		14	

Centri SMILDLa partecipanti alla Survey multicentrica del 2010 riferita all'anno di attività 2009

Aquila, Forlì, Gallarate, Milano, Nuoro, Padova, Palermo, Pescara, Pistoia, Prato, Reggio Emilia, Roma, Sassari, Sassari 2 (Ozieri) **Venezia, Verona, Viterbo, Trieste** (# 18)

Stefanutti C, LIPIDCLUB & Therapeutic Apheresis 2010


Structure of the Aorta
Arch
Ascending Aorta
Root
Coronary Arteries
Descending Aorta
Heart
Diaphragm
Celiac Artery
Superior Mesenteric Artery
Renal Arteries
Inferior Mesenteric Artery
Abdominal Aorta
Iliac Arteries


Aortic Valve

Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis

Claudia Stefanutti, Antonio Vivenzio, Serafina Di Giacomo, Bruno Mazzarella, Giovanna Bosco, and Andrea Berni

doi: 10.1111/j.1537-2995.2009.02135.x
TRANSFUSION 2009;49:1461-1470.
Volume 49, July 2009 TRANSFUSION

UNIROMA1 'La Sapienza' – Therapeutic Plasmapheresis Unit

AORTA AND CORONARY ANGIOGRAPHIC FOLLOW-UP OF CHILDREN WITH SEVERE HYPERCHOLESTEROLEMIA TREATED WITH LDL APHERESIS

#	Patient	Clinical diagnosis	
1	MD	HomFH	L.Ph. IIa
2	RM	DHFH	L.Ph. IIa
3	YR	DHFH	L.Ph. IIa
4	ST	HomFH	L.Ph. IIa
5	ED	HomFH	L.Ph. IIa
6	EAL	HomFH	L.Ph. IIa
7	GP	HomFH	L.Ph. IIa
8	GL	HomFH	L.Ph. IIa
9	DMV	DHFH	L.Ph. IIa
10	DG	DHFH	L.Ph. IIa
11	BG	ARH	L.Ph. IIa

HomFH: Homozygous Familial Hypercholesterolaemia
DHFH : Double Heterozygous Familial Hypercholesterolaemia
ARH : Autosomal Recessive Hypercholesterolaemia
L.Ph. : Lipoprotein Phenotype

Stefanutti C, Transfusion 2009; 49(7): 1461-1470

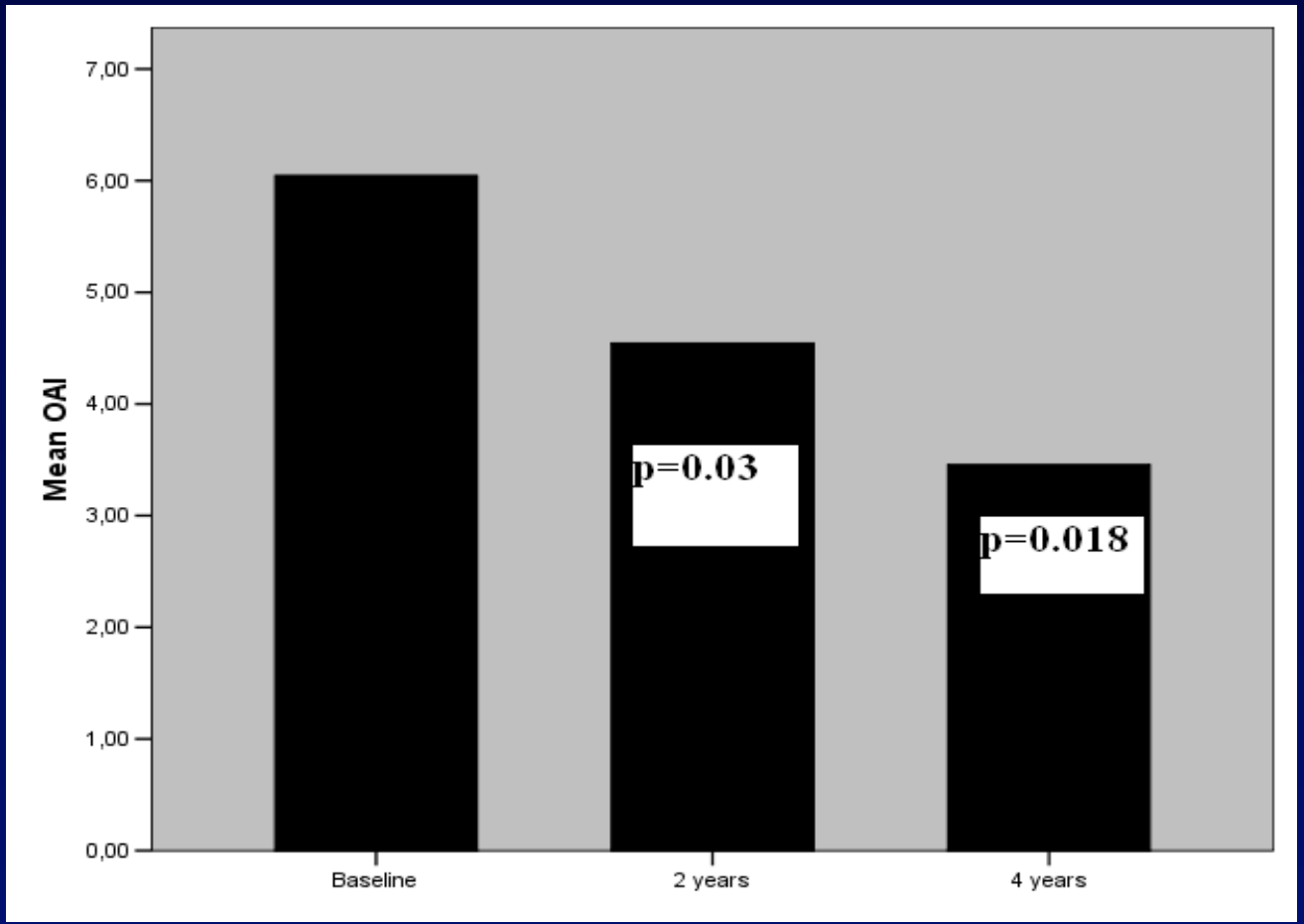
Table 3. Mean levels of TC, LDLC, HDLC, and TG in plasma, at baseline, and on treatment with LDLa

	TC^	TG	HDLC	LDLC
Baseline	826.1±183.3	103.8 ±37.6	39.1 ± 9.2	767.8 ± 181.9
Before LDLa	344.8 ± 66.8 ***	76.9 ± 26.7 **	45.9 ± 6.2 *	311.3 ± 22.8 ***
After LDLa	122.6 ± 24.4 ***	28.3 ± 12.8 ***	42.1 ± 2.2 ns	79.1 ± 20.7 ***

^: mg/dL; All data are expressed as mg/dL; mean ± SD.
*: p≤0.03; **: p≤0.04; ***: p≤0.001; ns: not significant.

Stefanutti C, Transfusion 2009; 49(7): 1461-1470

Figure 1. Overall Atherogenic Index (OAI) at baseline, and after 2 and 4 years from the beginning of treatment with LDLa.



Stefanutti C, Transfusion 2009; 49(7): 1461-1470

The OAI score at baseline was significantly co-related to the basal values of TC (P = 0.015), LDLC (P = 0.015), and TG (P = 0.01). but not of HDLC (P = 0.075) as demonstrated by the logit regression analysis. The model highlighted a Cox and Snell pseudo-R2 of 0.67

Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events

Beate R Jaeger et al.Nature Clinical Practice Cardiovascular Medicine 2009; 6(3):229-239

- longitudinal, multicenter, cohort study
- Eligible patients had coronary artery disease and Lp(a) levels ≥2.14 µmol/l (95th percentile)
- # 120 patients; mean duration of lipid-lowering therapy alone: 5.6 ± 5.8 years; mean duration of apheresis was 5.0 ± 3.6 years
- **Systems used**: HELP, DALI, dextran-sulfate (LIPOSORBER), double filtration, immune adsorption (Plasmaselect/Therasorb), and Excorim (anti Lp(a) antibody)
- Median Lp(a) concentration was reduced from 4.00 µmol/l to 1.07 µmol/l with apheresis treatment (P <0.0001); the corresponding mean annual MACE rate per patient was 1.056 versus 0.144 (P <0.0001)
- Lowering of Lp(a) levels by apheresis was efficacious and safe. Reccomended for patients in whom maximally tolerated doses of medication alone have failed to control coronary artery disease-associated events

Treatment of symptomatic HyperLp(a)lipoproteinemia with LDL-apheresis: a multicentre study

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Atherosclerosis Suppl. 2009; 10 (5): 89-94 **doi:10.1016/S1567-5688(09)71819-7**

Table 2. Current age, age at beginning of drug treatment, LDLa and time under LDLa

Centre	Current age # 19	Age at drug treatment start	Age at first LDLa treatment	Duration of treatment with LDLa
VERONA	57	45	56	1.1
PADOVA	41	34	35	5
PADOVA	41	25	30	11
PISTOIA	54	49	49	4.4
PISTOIA	63	44	61	2.1
PISTOIA	64	45	62	2
PISTOIA	66	49	65	1.3
PISTOIA	67	54	66	0.7
PISTOIA	62	62	62	0.2
REGGIO EMILIA	39	31	38	1.2
REGGIO EMILIA	61	59	59	2.3
REGGIO EMILIA	56	38	51	5.9
REGGIO EMILIA	59	44	58	1.2
ROMA	48	28	41	7
ROMA	52	48	49	4
ROMA	43	30	40	2.6
ROMA	45	40	43	3.4
ROMA	61	55	56	4.7
ROMA	45	45	45	0.4
Mean (years)	**53.89**	**43.42**	**50.84**	**3.18**
SD	**9.37**	**10.45**	**10.85**	**2.72**

~ 7 aa

Table 3. Mean plasma Lp(a) and LDLC levels at baseline, and before/after LDL-apheresis

Lp(a) mg/dL		
Baseline	172.3±153.8	
Before	124.5 ± 107.2	P ≤ 0.001
After	34.2± 40.6	P< 0.001
LDL C mg/dL		
Baseline	152.3±74.6	
Before	130.4 ± 61.1	P = 0.004
After	41.2 ± 25.1	P < 0.001

OUTCOME

Patients with coronary artery disease (CAD) submitted to coronary catheterization before LDLa were 95%. 37% had both CAD and extra-coronary artery disease.

79% were submitted to coronary revascularization before LDLa. CAD was: monovasal in 8 patients (42.1%), bivasal in 5 (26.4%), trivasal in 4 (21%), plurivasal in 2 (10.5%).

In 94.5% of the sample the lesions were stable (< 0% deviation) over 3.1±2.7 years. In 5.5% (# 1) CAD recurred despite treatment with LDLa.

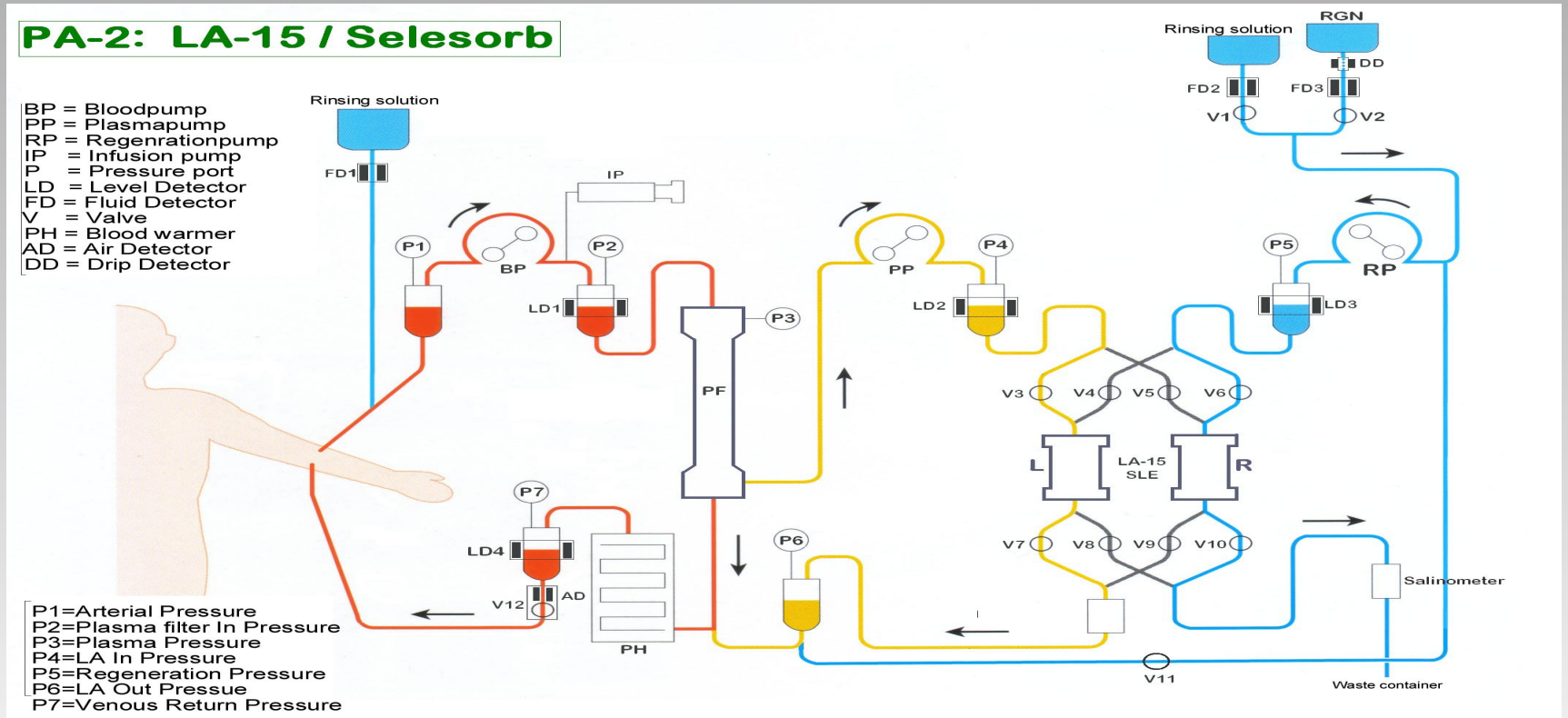
CONCLUSION

This multicentre study confirmed that long-term treatment with LDLa was at least able to stabilize CAD in the majority of the individuals with symptomatic HyperLp (a)lipidemia.

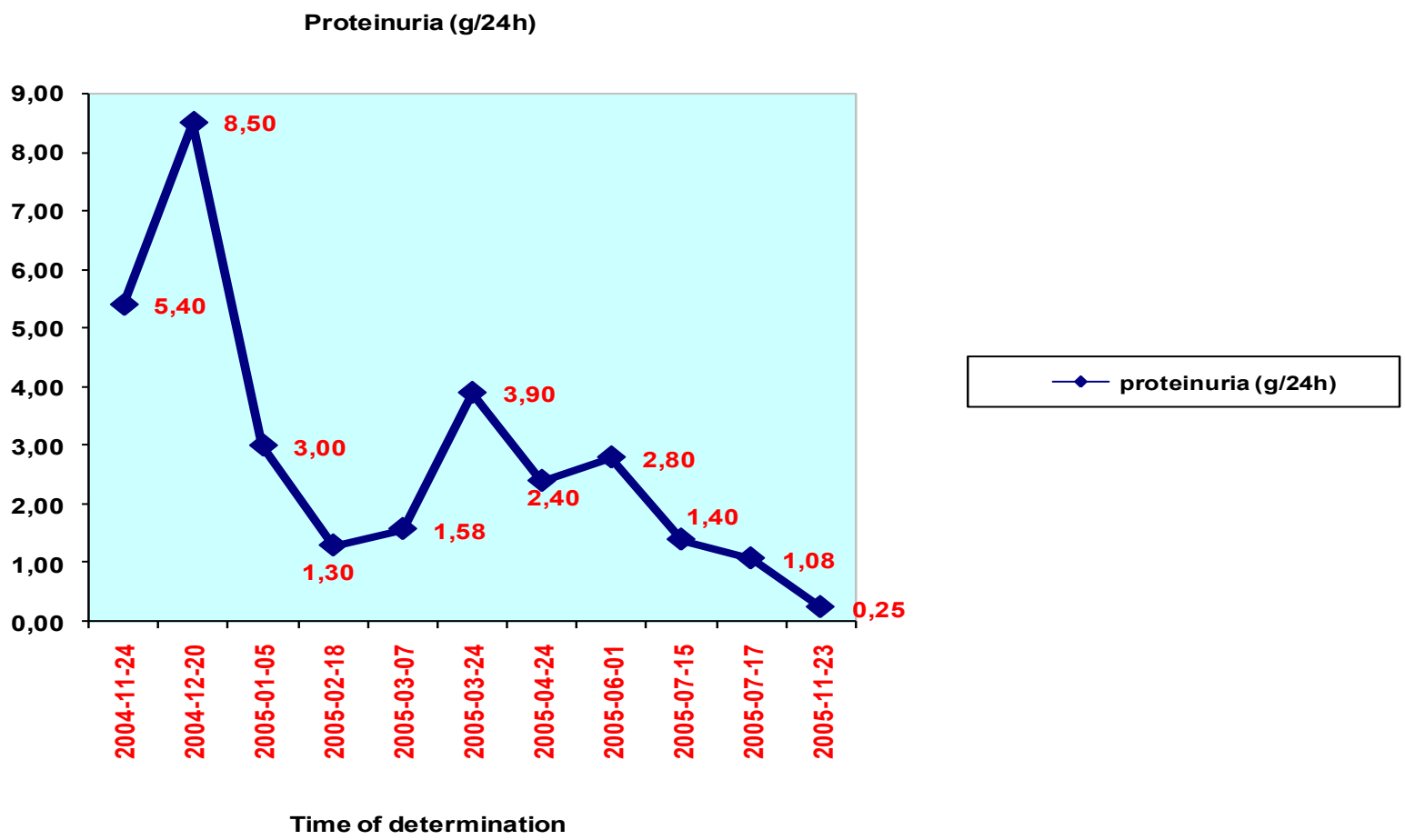
Therapeutic Plasmapheresis in the Treatment of Complicated Systemic Lupus Erythematosus

Stefanutti C., et al (2008):
Therapeutic plasmapheresis in the treatment of complicated Systemic Lupus Erythematosus. In:
"Systemic Lupus Erythematosus Research Trends."
Frank Columbus Ed. Nova Science Publishers, Inc. New York, U.S.A.. In Press.

6 patients, 5 females and 1 male, (mean age: 39.5 years) with SLE, submitted to therapeutic plasmapheresis using Selesorb® immunoadsorption system



Patient PE affected by SLE: Progressive decrease of proteinuria (g/24 hours) after 1-year treatment with immunodsorption apheresis



C. Stefanutti et al, 2008

Immunoadsorption Apheresis and Immunosuppressive Drug Therapy in the Treatment of Complicated HCV-Related Cryoglobulinemia

C. Stefanutti,1* A. Vivenzio,1 S. Di Giacomo,1 G. Labbadia,1 F. Mazza,1 G. D'Alessandri,2 P.M. Ferraro,3 and C. Masala 1

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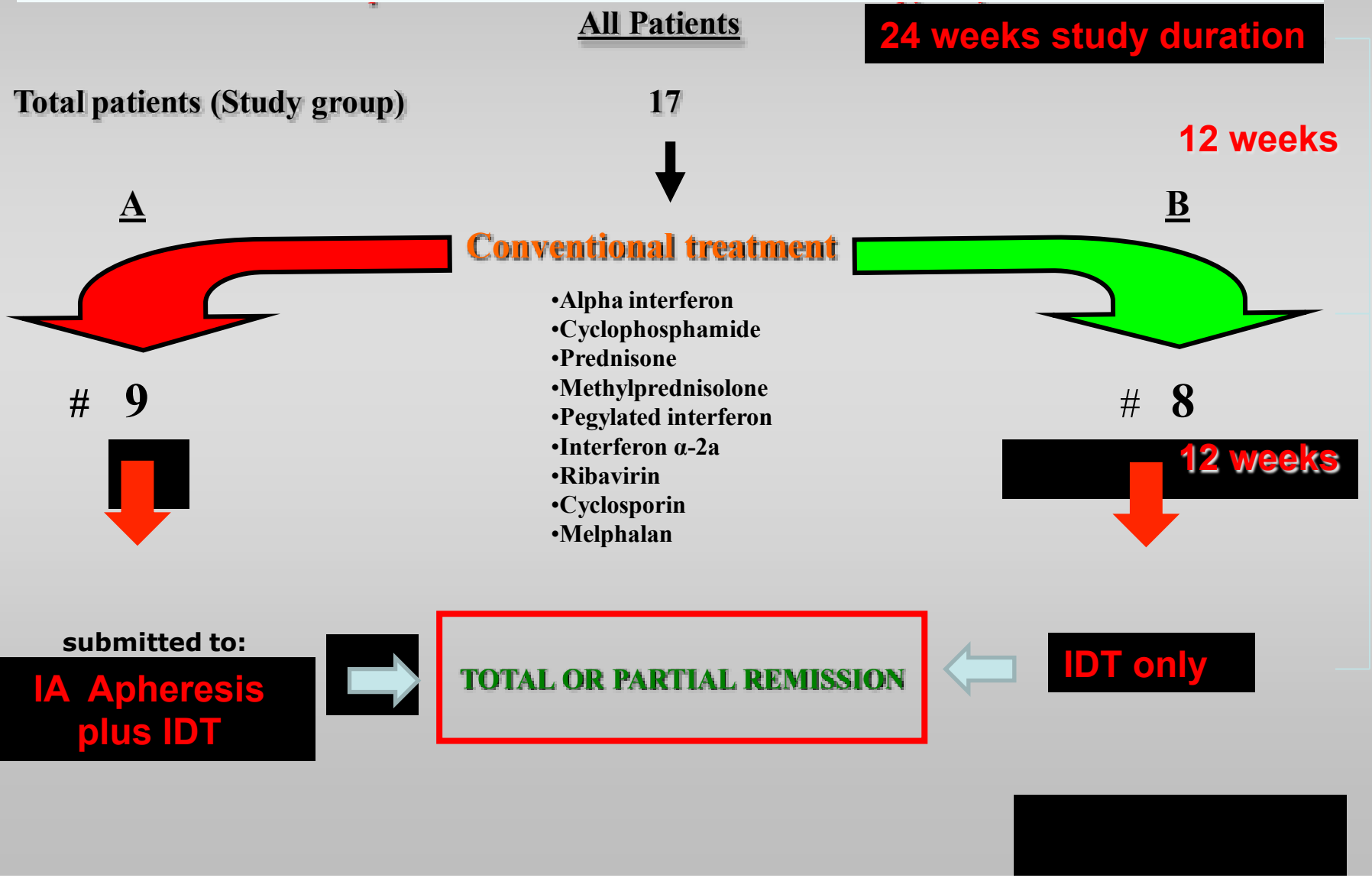
J Clin Apher. 2009;24(6):241-6. PMID: 19927363

Study design and course of treatment

All patients after "run in " period were assigned randomly in

Group A : Patients submitted to IA Apheresis plus drug

Group B: Patients submitted to medical therapy only



Clinical Score (CS)

At baseline CS0	Patients enrollment in the study
After 'run-in' CS1	After 12 weeks treatment with IDT
End of the study	After 24 weeks: Group A: IA + IDT (CSA) Group B: IDT only (CSB)

Clinical Score.
Statistical differences observed in the study

CS0	21.44 ±1.8	
CS1	22.13±1.9	*ns*
CS1	22.13±1.9	
CSA	10.0±0.7	P<0.001
CSB	12.1±2.2	*ns*
CSA	10.0±0.7	P= 0.03
CSB	12.1±2.2	

Outcome

Variazioni statisticamente significative rilevate: tra CSA e CS1 ($p \leq 0.001$) e tra CSA e CSB ($p = 0.03$). Le variazioni risultavano essere più favorevoli al gruppo (A: IA + IDT) randomizzato al trattamento combinato farmacologico-aferetico;

E' stata infatti osservata una percentuale statisticamente significativa più elevata di remissione delle tre più severe complicanze cliniche censite nello *scoring model* (ulcere degli arti inferiori, vasculiti ed ulcere cutanee con necrosi) nel gruppo A in confronto al gruppo B (80% *vs* 33%, rispettivamente) ($p \leq 0.05$).