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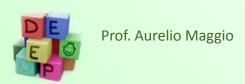
Review on Effectiveness and Safety of combination treatment with Deferoxamine (DFO) – Deferiprone(DFP) treatment

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MAIN AIMS

- Evaluation of effectiveness and safety on combined chelation treatment with DFO and DFP in patients with Thalassemia Major (TM) using three published meta-analysis studies;
- Review Italian cohorts studies on this kind of treatment;



WHY TO USE META-ANALYSIS STUDIES?

Using the levels of evidence for individual class assignments according to the ACC/AHA (Klocke et al, 2003)

Data derived from multiple randomised
clinical trials

- **B** Data derived from a single randomised trial, or from non randomised studies
- C Consensus opinion of expert



OUTCOMES CONSIDERED IN META-ANALYSIS STUDIES

EFFECTIVENESS

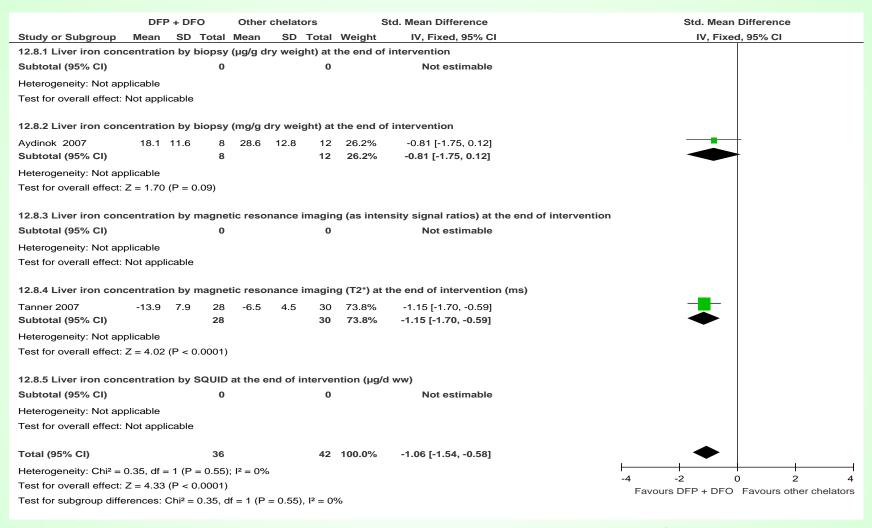
- Liver iron concentration as mean change from baseline
- Serum ferritin at the end of intervention
- Changes in Ejection fraction
- Changes in Urinary Iron Excretion

SAFETY

Side Adverse Events (SAEs)



LIVER IRON CONCENTRATION AT THE END OF INTERVENTION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS



Maggio A et Al. Iron chelation therapy in thalassemia major: a systematic review with meta-analyses of 1520 patients included on randomized clinical trials. Blood Cells Mol. Dis. 2011 Oct 15;47(3):166-75.

Prof. Aurelio Maggio

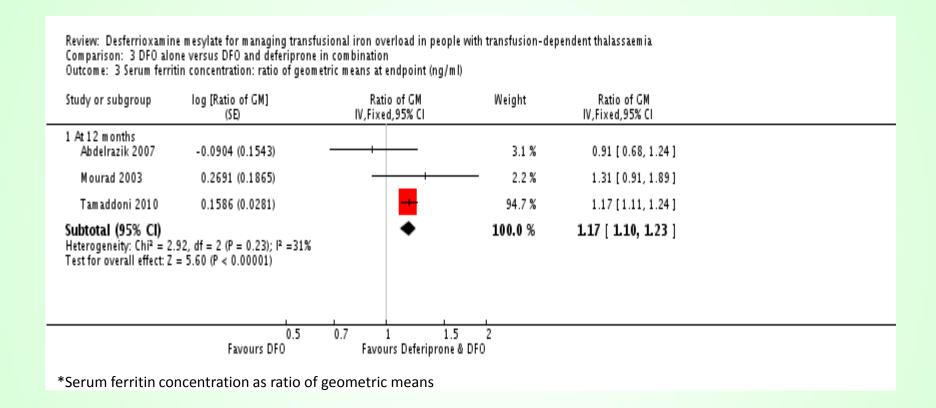
SERUM FERRITIN AT THE END OF INTERVENTION (NG/ML) IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS

	DF	P + DFO		Othe	r chelato	rs		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Aydinok 2007	2,954	2,765	8	3,209	2,279	12	5.2%	-255.00 [-2564.49, 2054.49]	
Gomber 2004	3,376.57	1,222.41	10	3,718.3	738.39	7	31.7%	-341.73 [-1276.20, 592.74]	
Mourad 2003	2,805	1,079.1	11	3,998	2,234.8	14	15.6%	-1193.00 [-2526.06, 140.06]	•
Tanner 2007	997	1,567	28	1,554	1,385	30	47.5%	-557.00 [-1320.22, 206.22]	-
Total (95% CI)			57			63	100.0%	-572.16 [-1098.32, -46.00]	•
Heterogeneity: Chi ² =	1.14, df = 3	3 (P = 0.77); I ² = 0)%				_	1000 0 500
Test for overall effect:	Z = 2.13 (F	P = 0.03)							-1000 0 500 Favours DFP + DFO Favours other chelator

Maggio A et Al. Iron chelation therapy in thalassemia major: a systematic review with meta-analyses of 1520 patients included on randomized clinical trials. Blood Cells Mol. Dis. 2011 Oct 15;47(3):166-75.



* SERUM FERRITIN AT THE END OF INTERVENTION (NG/ML) IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFO



Fisher SA et *Al* . *Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia*. Cochrane DatabaseSyst. Rev. 2013 Aug 21;8:CD004450.



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EJECTION FRACTION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS

	DFF) + DF	- 0	Other	chelat	tors		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	CI IV, Fixed, 95% CI
12.14.1 Ejection fract	ion at th	e end	d of int	erventic	on				
Aydinok 2007	72.6	6.6	8	67.4	9.8	12	12.9%	5.20 [-1.99, 12.39]	ı -
Tanner 2007	68.4	4.7	28	65.3	6	30	87.1%	3.10 [0.34, 5.86]	
Subtotal (95% CI)			36			42	100.0%	3.37 [0.79, 5.95]	1
Heterogeneity: Chi ² =	0.29, df =	= 1 (P	= 0.59); I ² = 0%	6				
Test for overall effect:	Z = 2.56	(P =	0.01)						
12.14.2 Ejection fract	ion as v	ariati	on bet	ween ba	aseline	and er	nd of inte	rvention	
Subtotal (95% CI)			0			0		Not estimable	е
Heterogeneity: Not app	olicable								
Test for overall effect:	Not appl	icable)						
									-20 -10 0 10 20 Favours other chelators Favours DFO + DFP
Test for subgroup diffe	rences:	Not a	pplicab	le					i avodis otilei cilelatois - Favodis DFO + DFP

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EJECTION FRACTION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFO

Review: Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia Comparison: 3 DFO alone versus DFO and deferiprone in combination Outcome: 1 Left ventricular ejection fraction: mean at endpoint (%) Study or subgroup DFO DFO and Deferiprone Mean Difference Weight Mean Difference Mean(SD) Mean(SD) IV, Fixed, 95% CI IV, Fixed, 95% CI Ν 1 At 12 months 78.04 (4.12) Abdelrazik 2007 69.02 (6.05) 52.7 % -9.02 [-11.64, -6.40] Tanner 2007 68.4 (4.7) 65.3 (6) 47.3 % -3.10 [-5.86, -0.34] 30 Subtotal (95% CI) 58 100.0 % -6.22 [-8.12, -4.32] Heterogeneity: $Chi^2 = 9.28$, df = 1 (P = 0.002); $I^2 = 89\%$ Test for overall effect: Z = 6.41 (P < 0.00001) -5 -10 10 Favours DFO & Deferiprone Favours DFO

Fisher SA et *Al* . *Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia*. Cochrane DatabaseSyst. Rev. 2013 Aug 21;8:CD004450.



URINARY IRON EXCRETION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS

Outcome 5 Urinary Iron Excretion

(a) Associated deferiprone plus deferoxamine versus other chelators

	DFF	+ DF(0	Other	chelat	210	S	td. Mean Difference	Std.	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV.	Fixed, 95% CI
12.12.1 Urinary iron	excretio	n (mg	kg/day)				400	- i	7 7 7 7
Aydinok 2007 Subtotal (95% CI)	0.88	0.32	8	0.38	0.22	12 12	46.3% 46.3%	1.82 [0.72, 2.91] 1.82 [0.72, 2.91]		
Heterogeneity: Not as	plicable									
Test for overall effect	Z = 3.26	(P = (0.001)							
12.12.2 Urinary iron	excretio	n (mg	day)							
Gomber 2004 Subtotal (95% CI)	7.37	1.89	10 10	5.83	1.65	7	53.7% 53.7%	0.81 [-0.20, 1.83] 0.81 [-0.20, 1.83]		
Heterogeneity: Not as	plicable									
Test for overall effect	Z = 1.57	(P = 0	0.12)							
Total (95% CI)			18			19	100.0%	1.28 [0.53, 2.02]		•
Heterogeneity: Chi ² =	1.74, df	= 1 (P	= 0.19)	$ ^2 = 43$	%					-
Test for overall effect	Z = 3.37	(P = 0	(8000.0						-4 -2	0 2 4
Test for subgroup dif	ferences	Chi?	= 1.74.	df = 1 (F	0.19	3), $P = 4$	2.6%		Favours other chel	ators Favours DFP + DF0

(b) Sequential deferiprone and deferoxamine versus deferoxamine

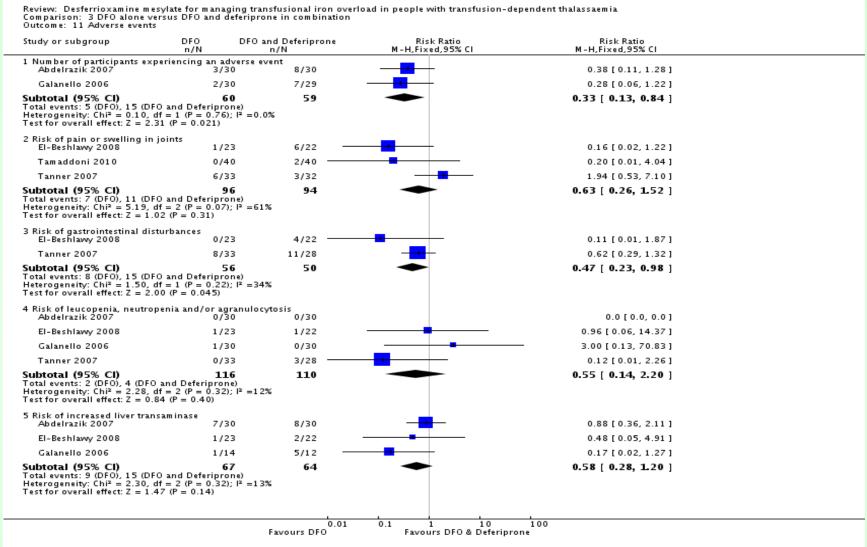
	Sequent	ial DFP +	DFO	Other	chelat	ors		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
13.12.1 Urinary iron 6	excretion (r	ng/kg/da	y)						
Abdelrazik 2007 Subtotal (95% CI)	0.76	0.49	30 30	0.53	0.21	30 30	100.0%	0.23 [0.04, 0.42] 0.23 [0.04, 0.42]	-
Heterogeneity: Not ap	plicable								
Test for overall effect	Z = 2.36 (P	= 0.02)							
13.12.2 Urinary iron e	excretion (r	ng/day)							
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not ap	plicable								
Test for overall effect.	Not applica	able							
Total (95% CI)			30			30	100.0%	0.23 [0.04, 0.42]	-
Heterogeneity: Not ap	plicable							H	- + +
Test for overall effect.	Z = 2.36 (P	= 0.02)						-1	1 -0.5 0 0.5 1
Test for subgroup diff	erences: No	ot applica	able						Favours other chelators Favours sequentialDFP+DF

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ADVERSE EVENTS IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFO



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ADVERSE EVENTS IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFP

Review: Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia

Comparison: 2 DFO and deferiprone in combination compared with deferiprone alone Outcome: 10 Adverse Events Study or subgroup Deferiprone and DFO Deferiprone Risk Ratio Weight Risk Ratio M-H,Fixed,95% CI M-H,Fixed,95% CI n/N 1 Risk of pain or swelling in joints 1/9 Aydinok 2007 0/12 3.2 % 3.90 [0.18, 85.93] EI-Beshlawy 2008 6/22 8/21 59.7 % 0.72 [0.30, 1.71] Maggio 2009 5/65 6/88 37.2 % 1.13 [0.36, 3.54] Subtotal (95% CI) 96 121 100.0 % 0.97 [0.50, 1.90] Total events: 12 (Deferiprone and DFO), 14 (Deferiprone) Heterogeneity: $Chi^2 = 1.31$, df = 2 (P = 0.52); $I^2 = 0.0\%$ Test for overall effect: Z = 0.09 (P = 0.93) 2 Risk of gastrointestinal disturbances El-Beshlawy 2008 4/22 7/21 34.5 % 0.55 [0.19, 1.60] Maggio 2009 7/65 16/88 65.5 % 0.59 [0.26, 1.36] Subtotal (95% CI) 109 100.0 % 0.58 [0.30, 1.11] Total events: 11 (Deferiprone and DFO), 23 (Deferiprone) Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.90); $I^2 = 0.0\%$ Test for overall effect: Z = 1.64 (P = 0.10) 3 Risk of leucopenia, neutropenia and/or agranulocytosis Avdinok 2007 1/9 1/12 6.2 % 1.33 [0.10, 18.57] El-Beshlawy 2008 1/22 1/21 7.4 % 0.95 [0.06, 14.30] Maggio 2009 15/65 14/88 86.4 % 1.45 [0.75, 2.79] Subtotal (95% CI) 121 100.0 % 1.41 [0.76, 2.61] Total events: 17 (Deferiprone and DFO), 16 (Deferiprone) Heterogeneity: $Chi^2 = 0.09$, df = 2 (P = 0.96); $I^2 = 0.0\%$ Test for overall effect: Z = 1.08 (P = 0.28) 4 Risk of increased liver transaminase Maggio 2009 22/65 23/88 95.0% 1.29 [0.79, 2.11] El-Beshlawy 2008 1/21 5.0 % 3/22 2.86 [0.32, 25.40] 109 100.0 % Subtotal (95% CI) 1.37 [0.85, 2.21] Total events: 25 (Deferiprone and DFO), 24 (Deferiprone) Heterogeneity: $Chi^2 = 0.49$, df = 1 (P = 0.48); $I^2 = 0.0\%$ Test for overall effect: Z = 1.30 (P = 0.19)0.01 100 0.1 10 Favours DFO & Deferiprone Favours Deferiprone

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DEFERIPRONE AND DEFEROXAMINE COMBINED CHELATION TREATMENT: PUBLISHED SCHEDULES OF ADMINISTRATION

	Interventions	
Study	Dosage of DFP (mg/kg/day)	Dosage of DFO (mg/kg)
Aydinok, 2005	75 for 7 days/week	40-50 for 2 days/week
Abddelrazik, 2007	75 for 4 days/week	40 for 2 days/week
Gomber, 2004	75 in 2-3 diveded doses	40 for 2 days/week
Tanner, 2007	75 in 2-3 divided doses	40-50 for 5 days/week
El-Beshlawy, 2008	60-83 for 7 days/week	23-50 for 2 days/week
Ha, 2006	75 in 3 divided doses for 7 days/week	30-60 for 2 days/week
Mourad, 2003	75 in 3 divided doses for 7 days/week	Total of 2 gr for 2 days/week
Tamaddoni, 2010	75 for 7 days/week	40-50 for 2 days/week
Galanello, 2006	25 weight 3xdaily for 5 days/week	20-60 for 2 days/week



SUMMARY STATISTICS OF B-THALASSEMIA MAJOR PATIENTS FROM MIOT

Overall TM patients scanned/evaluated	1658/1548
Mean follow-up (months)	$42,91 \pm 20,36$
Dead	23
Causes of death	
Heart failure	11
Cardiac arrest	3
Liver cirrhosys	1
TMO complication	1
Pulmonary embolism	1
Hepatocellular carcinoma	1
HCC	1
Lymphoma	1
Liver failure	1
NND septic shock	1
Car accident	1



VALIDATION OF MAGNETIC RESONANCE T2* TECNIQUE BASED ON ITALIAN POPULATION

	Global heart T2* (CoV %)	Mid-ventricular septum T2* (CoV %)	Liver T2* (CoV %)
Ancona	9,9	15,2	12,8
Campobasso	11,2	12,7	13,5
Catania	9,8	7,7	9,6
Palermo	7,7	7,1	17,9
Roma	4,2	22,2	10,3
All sites	8,9	14	14
All sites T2* < 20 ms	9,3	10,5	11,7
All sites T2* > 20 ms	7,9	12,8	10,2

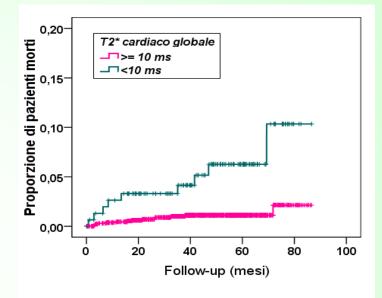
Ramazzotti A, Pepe A, Positano V, Rossi G, De Marchi D, Brizi MG, Luciani A, Midiri M, Sallustio G, Valeri G, Caruso V, Centra M, Cianciulli P, De Sanctis V, Maggio A, Lombardi M. *Multicenter validation of the magnetic resonance T2* technique for segmental and global quantification of myocardial iron*. J Magn Reson Imaging. 2009 Jul;30(1):62-8. doi: 10.1002/jmri.21781.

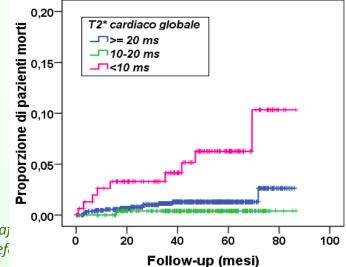


UNIVARIATE COX-REGRESSION MODEL FOR ASSESSING RISK OF DEATH IN 1548 TM PATIENTS UNDER MIOT

	n (%)	n° death (%)	HR (95% CI)	p-value
Cardiac T2*, ms				
< 10 ms	156 (10,1)	9 (5,8)	5,24 (2,26-12,15)	< 0.0001
\geq 10	1392 (89,9)	14(1,0)	Reference	
< 20 ms	421 (27,2)	10(2,4)	1,85 (0,81-4,24)	0,143
\geq 20 ms			Reference	
< 10 ms	- 156 (10,1)	9 (5,8)	4,48 (1,91-10,52)	0,001
10-20 ms	265 (17,1)	1 (0,4)	0,29 (0,04-2,27)	0,242
\geq 20 ms	1127 (72,8)	13 (1,2)	Reference	

	n (%)	n° death (%)	HR (95% CI)	p-value
Liver T2*, ms	_			
< 1.8 ms	292 (18,9)	7 (2,4)	1,80 (0,74-4,39)	0,193
	1253			
\geq 1.8 ms	(81,1)	16(1,3)	Reference	





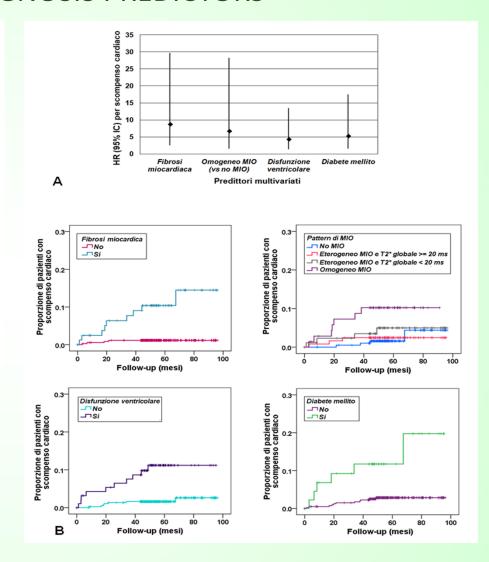


Review on Effectiveness and Saj with Deferoxamine (DFO) – Def

MULTIVARIATE COX ANALYSIS FOR HEART FAILURE ON INDIPENDENT PROGNOSIS PREDICTORS

Figure A	n (%)	HR (95% CI)	p-value
Myocardial fibrosis	<u> </u>		
Yes	82 (19,0)	8,81 (2,62; 29,57)	<0,0001
No	350 (81,0)	reference	
Hom ogeneous MIO			
Yes	71 (14,8)	6,76 (1,62;28,12)	0,009
No	198 (41,2)	reference	
Mild Left Ventricular			
dysfunction (<57%)			
Yes	96 (20,3)	4,36 (1,42; 13,35)	0,01
No	377 (79,7)	reference	
Diab etes m ellitus			
Yes	44 (9,8)	5,34 (1,64;17,41)	0,006
No	407 (90,2)	reference	

Figure B, <u>Log-rank</u> test: p<0,0001 p=0,016 p<0,0001 p<0,0001





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DEMOGRAPHICS SUMMARY STATISTICS OF 652 MR SCANNED B-THALASSEMIA MAJOR PATIENTS FROM UK HEMATOLOGY CENTERS

Demographics Total patients as	652
Total patients, n	17
excluded for heart failure/arrhythmia at first MR scan	
Age	$27,1\pm 9,6$
Sex	M: 319, F: 333
Race/ethnicity, n	
White	296
South Asian	283
Chinese	23
Arabic	31
Black	19
Biochemistry	
Transfusional red blood cell input, mL-1·kg-1·y-1	113,9±49,7
Serum ferritin, µg/L	2231±1801
Liver T2* geometric mean (95%	3,6 (3,5-3,8)
CI), ms	
LV ejection fraction, %	66,1±8,5
Therapy	
Combined DFO+DFP (n=105, 16.1%)	
DFO, mg·kg·1·wk·1	160 (111, 235) for 4 (2, 5) d/wk
DFP, mg·kg-1·d-1	20 (12, 43,5)
Combined DFO-DFX	
DFX $(n=1, 0.2\%)$	167 for 5 d/wk
DFO, mg·kg·l·d·l	20
DFO alone (n=433, 66.4%) mg·kg-1·wk-1	202 (164, 270) for 5 (5, 5) d/wk
DFP alone (n=72, 11,0%) mg·kg·l·d·l	70 (57, 82)
DFX alone (n=19, 2,9%) mg·kg ⁻¹ ·d ⁻¹	10 (7,5, 15)
No chelation, n (%)	22 (3,4)

Kirk, P et Al. Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major. Circulation 2009. 120: 1961-1968.



RELATIVE RISK OF HEART FAILURE FOR CARDIAC AND LIVER T2* AND FOR SERUM FERRITIN LEVELS INCLUDING MULTIPLE SCANS OF THE 652 PATIENTS INCLUDED IN THE STUDY

	n	n° heart failure	RR	p-value
Cardiac T2*, ms				
<6	72	34	270	< 0,001
6 to <8	98	29	171	< 0,001
8 to <10	108	15	81	< 0,001
≥ 10	1164	2	Reference	
Liver T2*, ms				
< 0,96	63	3	1,25	0,74
0,96 to < 1,4	136	14	2,59	0,021
1,4 to < 2,7	382	26	1,68	0,13
2.7 to < 6.3	484	22	1,22	0,57
\geq 6,3	377	15	Reference	
Ferritin, µg/L				
≥ 2500	450	35	0,56	0,02
< 2500	992	45	Reference	ŕ

Kirk, P et Al. Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major. Circulation 2009. 120: 1961-1968.



MAIN RESULTS OF THE REVIEW USING META-ANALYSIS STUDIES

Effectiveness

- Combination treatment is able to have advantage versus Deferoxamine alone in term of:
- Decreasing of Liver Iron Concentration
- Serum Ferritin Levels
- Increasing of Left Ventricular Ejection Fraction
- Urinary Iron Excretion

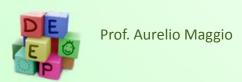
Safety

 Combination treatment does not have more SAEs in comparison with Deferiprone alone at dosage used in randomized clinical trials



SUGGESTIONS DERIVED FROM THESE FINDINGS (A)

- A) Effectiveness and Safety of Combined Chelation Treatment is well shown using Level A of Evidence (Klocke et al, 2003)
- B) Effectiveness of Combined treatment was shown both in decreasing Liver Iron Concentration and increasing Left Ventricular Ejection Fraction
- C) No data on literature have been reported using Deferiprone and Deferoxamine treatment for 7 days/week in combination. No data on literature have been reported using Deferiprone at 100mg/Kg per os for 7 days during combined chelation treatment.



SUGGESTIONS DERIVED FROM THESE FINDINGS (B)

- A) MIOT studies suggested as not all patients today have access to heart MRI (1658/7000 (23.6%) Italian patients had scanner for one Heart MRI)
- B) MIOT Multivariate Cox Analysis suggested as Myocardial Fibrosis is the most powerful predictor factor. Moreover, even mild Left Ejection Fraction (<57%) dysfunction and diabetes are independent predictor factors.
- C) Effectiveness of combination treatment in decreasing Liver Iron Concentration suggested to spread its use in patients with Liver Iron Overloading independently of Heart T2* signal.



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