

# **Intravitreal ranibizumab combined with oral supplementation with docosahexaenoic acid and antioxidants in diabetic macular edema**

Results at 36 months of a controlled, randomized, simple blinded clinical trial



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# Intravitreal ranibizumab combined with oral supplementation with docosahexaenoic acid and antioxidants in diabetic macular edema

Results at 36 months of a controlled, randomized, simple blinded clinical trial

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## Objectives

Evaluate long term efficacy of intravitreal ranibizumab combined with dietetic supplementation of docosahexaenoic acid (DHA) in patients suffering diabetic macular edema (EMD).

## Methods

The trial was randomized and simple-blinded. A total of 28 patients (33 eyes) received intravitreal ranibizumab (0,5 mg) combined with DHA (1.050 mg/day) and 32 patients (41 eyes) received ranibizumab alone (control group). Was evaluated the central subfield macular thickness of the retina (CSMT), the best corrected visual acuity (BCVA, ETDRS letters), profile of fatty acids in the red blood cell membrane, and the number of intravitreal injections. The variables of each group were compared with a mixed linear model (covariable: basal measurement; randomized factor: the patient).

## Results

After 24 months, the difference in CSMT reduction was significantly in favor of the supplemented group (the difference IC 95%, 7,20-97,66;  $P=0,024$ ), maintaining the significance ( $P<0,05$ ) at months 25, 30, 33 and 34 (at month 36, CSMT was:  $275\pm 50\ \mu\text{m}$  vs.  $310\pm 97\ \mu\text{m}$ ). No differences were detected in BCVA between

the supplemented group and the control group (24 months:  $42,2\pm 9,2$  vs.  $40,1\pm 10,0$ ; 36 months:  $41,9\pm 10,4$  vs.  $41,3\pm 9,7$ ). The total number of injections was  $13,1\pm 7,0$  in the supplemented group and  $10,6\pm 6,0$  in the control group ( $P=NS$ ). It was detected a tendency towards an improvement in the metabolic control (HbA1c) for the supplemented group, but a worsening tendency for the control group, with significant differences between groups at 36 months in favor of the supplemented group ( $P<0,035$ ). From year to year there were significant improvements in the serum Total Antioxidant Capacity of the supplemented group (12 months:  $96,5\pm 20,3$  vs  $94,3\pm 29,5$ ; 24 months:  $124,7\pm 38,7$  vs  $104,1\pm 19,8$ ; 36 months:  $145,4\pm 49,8$  vs  $106,3\pm 22,3$ ), with significant differences between groups at 36 months in favor of the supplemented group ( $P<0,001$ ). Relating DHA incorporation into red blood cell membranes, it was detected a persistent increase in its concentration from the basal situation and up to 36 months in the supplemented group, being differences significant at 12 and 24 months, with significant differences between groups at 36 months in favor of the supplemented group ( $P<0,001$ ).

## Conclusions

The anatomic improvement seen in DME detected by a reduction in the CSMT is associated to the combined treatment with intravitreal ranibizumab plus DHA supplementation, and is maintained after 36 months of follow up period.



## OBJECTIVES

### MAIN OBJECTIVE

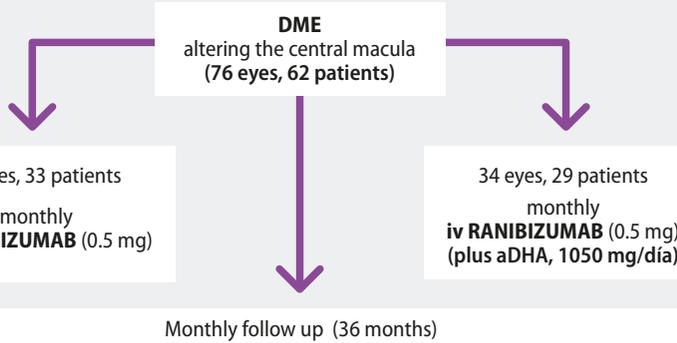
To evaluate **CMT, BCVA** and **number of injections** in patients suffering DME treated with intravitreal Ranibizumab plus oral **DHA (highly concentrated)** supplementation. During 36 months.

### SECONDARY OBJECTIVES

- Evaluate supplementation influence on the **metabolic control (HbA1c)**.
- Evolution of **oxidative stress markers (TAC)**.
- Evaluate **bioavailability of supplement**. Profile of fatty acids in red blood cell membrane.

Results at 36 months of the different analyzed variables:

- Central Macular Thickness (OCT)
- Visual Acuity (ETDRS)
- Number of Ranibizumab injections
- Metabolic Control (HbA1c)
- Oxidative stress markers TAC
- PUFA levels in red blood cell membranes

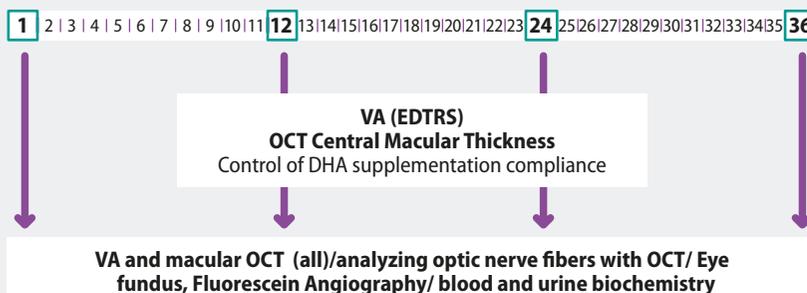


Randomized, simple blind design.

All patients receiving intravitreal Ranibizumab injections, and one group is randomized to receive DHA-TG 1g/day (BrudyRetina: 3 capsules/day) of Tridocosahexaenoia-AOX®.

Monthly visits up to 36 months of follow up.

## REGIMEN OF VISITS 1st, 2nd, 3rd YEAR



A regimen of monthly visits up to 36 months evaluating:

- Visual Acuity
- Central Macular Thickness
- Bringing the empty boxes at each visit as a control of compliance.

Other tests being performed every 6 months, if necessary.

## RESULTS • DEMOGRAPHIC CHARACTERISTICS

62 patients (76 eyes)	Control	Supplemented
<b>Sex</b> Women (33.8%) Men (66.2%)	37.5% 62.5%	29.4% 70.6%
<b>Age 67</b> (52-82)	67	67
<b>Years of DM-2 evolution</b> (>10 years - 84%)	5-25	5-25
<b>Metabolic control</b> HbA1c (7.6%)(6-12.3)	7.5%	7.7%

Homogeneous distribution of groups.

Average age of 67 years.

Type II diabetes;  
84% with evolution > 10 years.

## INTRAVITREAL INJECTIONS REGIMEN



### TREATMENT

VA reduced due to **DME affecting the central macula. Monthly Ranibizumab**, until reaching VA stability in 3 consecutive visits.

BCVA  $\neq$  5 L  
CMT > 100  $\mu$ m



### RE TREATMENT

When stability is lost (difference in **VA of more than 5 L**) or OCT thickness is increasing  $\geq$  **100 microns**

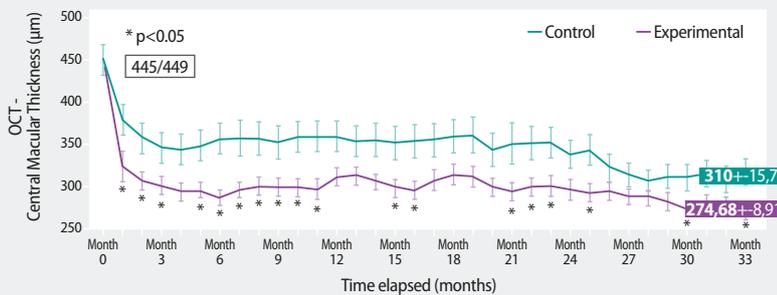
Onset of treatment with a monthly injection for the first 4 months reaching thickness stability.

Injecting again when reading capacity (EDTRS) has worsened in > 5 letters.

Or in case that Central Macular Thickness is increased > 100 microns.

## RESULTS • CMT

What changes we find in the CMT over the course of 36 months?



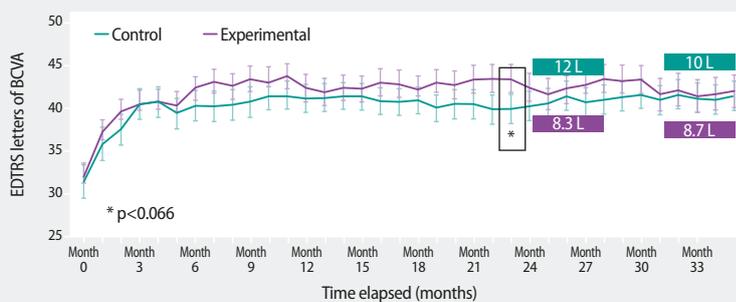
There is a sustained significant reduction of the central macular thickness in both groups at 12, 24 and 36 months.

There is significant reduction of central macular thickness additional to ranibizumab only in the supplemented group vs. the control group at 24 and 36 months, that is seen from the very first month ( $P < 0.035$ ).

Average reduction in the supplemented group is 175 microns vs. 135 microns in the control group at month 36.

## RESULTS • BCVA

How is the evolution of VA over the course of 36 months?



Results at 24 months show a tendency towards a significant improvement of the VA in the supplemented group ( $P < 0.066$ ), that has not been maintained in the last 12 months.

After 36 months, VA improvement has been of 10 letters for the supplemented group, and 9 letters for the control group.

## RESULTS • BCVA

How is the evolution of VA over the course of 36 months?



Analyzing the groups of improvement in VA acuity, differences in favor of the supplemented group can be seen in those improving > 5 letters, and a significant improvement in those improving > 10 letters.

The groups worsening VA (< 5 letters) in respect of the basal situation, the percentage of worsening is higher in the control group.

## RESULTS • NUMBER OF INJECTIONS

Average number of injections at 12, 24, and 36 months  
Number of injections is related with macular thickness at onset

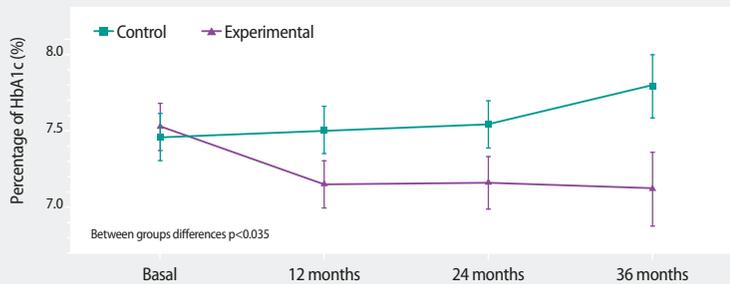
Initial VA	Metabolic control	Supplementation	
Initial CMT			
CMT	12 m	24 m	36 m
< 450 μm	6.5	7.7	9.6
> 450 μm	7.5	10.6	14.8
	P<0.004	P<0.0001	P<0.001

About the average number of iv ranibizumab injections, between group differences were not detected.

But it's clearly seen that patients showing lower macular thickness at onset (<450 microns) need less number of injections along the complete follow up period.

## RESULTS • HbA1c

Metabolic control (HbA1c)



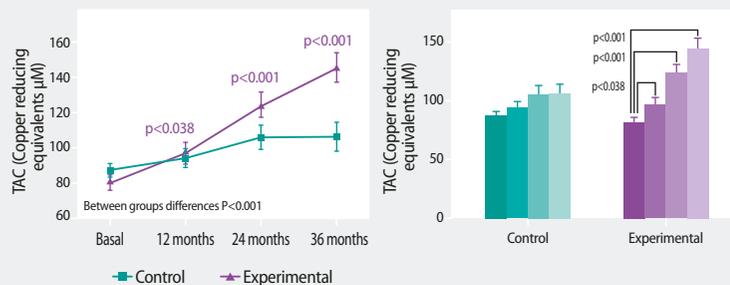
There is a clear tendency towards improvement in the metabolic control in the supplemented group after 24 months, which is maintained at 36 months.

Metabolic control in the control group tends to a worsening all a long the 36 months period.

At 36 months there are significant differences between both groups in favor of the supplemented group (P=0.035).

## RESULTS • Oxidative Markers

Serum total antioxidant capacity (TAC)

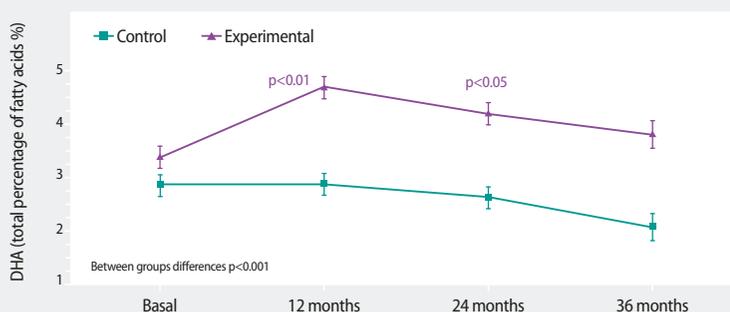


There is a significant difference in the serum Total Antioxidant Capacity in the supplemented group at 12 and 24 months, being maintained up to 36 months.

At 36 months between groups significant differences can be detected in favor of the supplemented group (P<0.001).

TAC: Total Antioxidant Capacity

## RESULTS • DHA Bioavailability



Concentration of DHA in the red blood cell membrane of the supplemented group is increased at 36 months, being significant at 12 and 24 months.

The membrane DHA levels in the control group tend to decrease after 36 months.

There are between groups significant differences at 36 months in favor of the supplemented group (P<0.001).

# Conclusions

Supplemented patients are reaching lower CSMT from the very first month starting supplementation when comparing with the control group, and the difference is maintained all along the 36 month of follow up.

Supplemented patients are showing an **improved metabolic control, improved TAC, and higher DHA availability in cell membranes.**

We conclude that **supplementation is being a benefit for patients suffering diabetic macular edema.**

(1) Lafuente M., et al; combined intravitreal ranibizumab and oral supplementation with docosahexaenoic acid and antioxidants for diabetic macular edema: two-year randomized single-blind controlled trial results; Retina 2016 Oct 26;1-10. DOI: 10.1097/IAE.0000000000001363.

## BRUDYMACULA

COMPOSITION	In 1 capsule	%RDA*
<b>Oil concentrated in Omega-3 fatty acids</b>		
22:6ω3, DHA (mg)	350	-
20:5ω3, EPA (mg)	42,5	-
22:5ω3, DPA (mg)	30	-
<b>Vitamins</b>		
Vitamin C (mg)	80	100
Vitamin E (mg α-ET)	12	100
<b>Minerals</b>		
Zinc (mg)	10	100
Copper (mg)	1	100
<b>Other nutrients</b>		
Lutein(mg)	5	-
Zeaxanthin (mg)	1,4	-

1 capsule/day = 350 mg DHA

\*RDA = Recommended daily allowances

## BRUDYRETINA 1,5g

COMPOSITION	1 cap.	%RDA*	3 cap.	%RDA*
<b>Oil concentrated in Omega-3 fatty acids</b>				
22:6ω3, DHA (mg)	350	-	1050	-
20:5ω3, EPA (mg)	42,5	-	127	-
22:5ω3, DPA (mg)	30	-	90	-
<b>Vitamins</b>				
Vitamin B1 (mg)	0,37	33	1,1	100
Vitamin B2 (mg)	0,47	33	1,4	100
Vitamin B3 (mgNE)	5,3	33	16	100
Vitamin B6 (mg)	0,47	33	1,4	100
Vitamin B9 (μg)	66,7	33	200	100
Vitamin B12 (μg)	0,83	33	2,5	100
Vitamin C (mg)	26,7	33	80	100
Vitamin E (mg α-TE)	4	33	12	100
<b>Minerals</b>				
Zinc (mg)	1,66	16,66	5	50
Copper (mg)	0,16	16,66	0,5	50
Selenium (μg)	9,16	16,66	27,5	50
Manganese (mg)	0,33	16,66	1	50
<b>Other nutrients</b>				
Lutein (mg)	3	-	9	-
Zeaxanthin (mg)	0,3	-	0,9	-
Glutathione (mg)	2	-	6	-

3 capsules/day = 1050 mg DHA

