PRELIMINARY ANALYSIS OF THE FINAL MULTICENTER INVESTIGATION OF RHEOPHERESIS FOR AGE RELATED MACULAR DEGENERATION (AMD) TRIAL (MIRA-1) RESULTS

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ABSTRACT

Purpose: To present an initial evaluation of the final data from the Multicenter Investigation of Rheopheresis for age-related macular degeneration (AMD) (MIRA-1) trial. This was a 12-month randomized, prospective, multicenter, double-masked, placebo-controlled, Food and Drug Administration approved clinical trial designed to compare rheopheresis treatment with placebo-control treatment.

Methods: Patients that had nonexudative age-related macular degeneration (AMD) and certain hemorheologic abnormalities were randomized to either rheopheresis or sham treatment in a 2:1 fashion. Best-corrected visual acuity was determined before and at 3, 6, 9, and 12 months following treatment. Adverse events were also recorded.

Results: A total of 216 patients were randomized. Of these, 18 were not included in the vision or adverse events evaluation because they did not complete one treatment. This decreased the number of patients that were evaluated for adverse events to 198 patients. In this group, there were 27 serious adverse events, but only 1.8 % of treatments were suspended because of adverse events. At 12 months, there were 104 treated patients and 63 placebo patients that had follow-up. The treated patients had a logMAR vision improvement of 0.02 ± 0.213, and the placebo patients had a vision improvement of 0.02 ± 0.20. This was not statistically significant (P = .977). The repeated measure P value for the entire time interval was not significant (P = .69). There appeared to be patients entered into the study that did not meet inclusion criteria. Excluding 37% of the treated patients and 29% of the placebo data from the analysis, there appeared to be statistically significant improvement in the treated patients compared to the control patients at 1 year with a P value of .001 (repeated measures P value = .01).

Conclusions: At best this was a flawed study in that 37% of the treated cases did not meet inclusion criteria, and at worst there was no evidence of effect. Even though the number of serious adverse events is small, because this study did not show an effect in the intent-to-treat group, rheopheresis should not be performed for AMD outside of an approved randomized controlled trial.

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INTRODUCTION

The Multicenter Investigation of Rheopheresis for age-related macular degeneration (AMD) (MIRA-1) trial is a 12-month randomized, prospective, multicenter, double-masked, placebo-controlled, Food and Drug Administration (FDA) approved clinical trial. It is designed to compare rheopheresis treatment with placebo-control treatment in over 150 patients with intermediate- to late-stage (AREDS grade 3 to 4, best-corrected visual acuity [BCVA] between 20/32 and 20/125 inclusive), high-risk (≥10 large soft drusen), nonexudative age-related macular degeneration (AMD) who also demonstrate the elevation of serum levels of select hemorheologic macromolecules. As such, MIRA-1 is the largest prospective, double-masked apheresis trial ever undertaken. A previous report on the interim results of the initial group of 43 randomized, intent-to-treat patients appeared to show some improvement in vision.[1] We present an initial analysis of the final data, which showed that there was no vision improvement in the treated group compared to the control but that in a subset of patients there may be the possibility of vision improvement that warrants further evaluation.

METHODS

SITES OF MIRA-1 STUDY

A total of 13 clinical centers in the United States have enrolled patients in this study. Before patient enrollment began at any center, the FDA and then the local institutional review boards of the participating clinical centers reviewed the protocol, authorized the patient informed consent, and accepted the clinical design. All ophthalmic and apheresis investigators, clinical coordinators, and photographers participated in a standardized orientation. Ophthalmic examiners assessed visual acuity using the ETDRS (logMAR) chart and a standardized refraction and visual acuity protocol. They underwent regular quality assurance audits by the study's independent clinical research organization, ProMedica International (Huntington Beach, California).

PATIENT SELECTION AND ENTRY EVALUATIONS FOR MIRA-1 STUDY

The FDA had initially authorized up to 180 patients for enrollment with the goal of having at least 150 evaluable patients at the conclusion of the trial. They then increased the enrollment numbers to allow for 185 evaluable patients. All patients provided informed consent. Ophthalmologists responsible for enrolling patients and follow-up determined ophthalmic eligibility criteria and supervised efficacy assessments. Nephrologists who were certified to enroll and follow the patients performed enrollment physicals, determined medical eligibility criteria, supervised treatments, and provided safety assessments. The inclusionary and exclusionary

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criteria for study eligibility are listed in Table 1. In addition, fundus photographs were obtained at baseline and at the 3-, 6-, 9-, and

TABLE 1. INCLUSION AND EXCLUSION CRITERIA FOR THE MULTICENTER INVESTIGATION OF RHEOPHERESIS FOR AMD (MIRA-1)

INCLUSION CRITERIA

- Patients can be any race and must be between the ages of 50 and 85 years inclusive.
- Patients must weigh ≥110 lb (50 kg).
- Study eye must have a diagnosis of nonexudative "dry" AMD with ≥10 large, soft, semisoft, and/or confluent drusen within 3,000 nm of the foveal center.
- Study eye must have a best-corrected visual acuity using the ETDRS chart between 20/32 and 20/125 inclusive.
- Geographic atrophy is allowed as long as it is less than three disc diameters outside of 3,000 nm of the foveal center.
- Serous pigment epithelial detachment is allowed as long as no clearly identifiable neovascularization is present.
- Patients must have elevated baseline concentrations of two of the following three rheologic factors: total serum cholesterol level ≥200 mg/dL, fibrinogen level ≥300 mg/dL, or serum immunoglobulin A (IgA) level ≥200 mg/dL, as determined at the qualifying evaluation.
- Patients must have a score of no more than 75 on the VFQ-25 Visual Functioning Questionnaire.
- Study eye must not have conditions that limit the view of the fundus.
- Patients must have normal prothrombin and partial thromboplastin clotting times with the exception of patients who are stable on long-term Coumadin therapy.
- Patients must have adequate bilateral antecubital venous access.
- Patients taking lipid-lowering medication at the beginning of the treatment phase must agree to continue to take it throughout the treatment phase using their current regimen.
- Patients must be available for minimum study duration of about 12 months.
- Patients must be highly motivated, alert, oriented, mentally competent, and able to understand and comply with the requirements of the study.
- Patients must agree to discontinue their previous vitamin regimen and to substitute their regimen with a uniform supplement regimen provided by the study, OcularRx (Science-Based Health, Corde Madera, California). This was done to ensure that every patient in the study ingested the same supplement regimen.

EXCLUSION CRITERIA

- Study eye with concomitant retinal or choroidal disorder other than AMD
- Study eye with significant central lens opacities
- Study eye with a diagnosis of exudative "wet" AMD.
- Study eye with other ocular diseases
- Patients who are in poor general health
- Patients with a hematocrit <35%, evidence of active bleeding, or a platelet count <100,000/L
- Patients with significant cardiac problems
- Patients with uncontrolled hypertension
- Patients with recent history of cerebral vascular disease
- Patients with severe hepatic failure or uncontrolled diabetes
- Patients with a history of HIV infection, AIDS, hepatitis, or other immunosuppressive disorders
- Patients who are allergic to fluorescein sodium and to indocyanine green
- Patients unwilling to adhere to visit or examination schedules
- Patients with a known history of alcoholism, drug abuse, or any other condition that would limit validity of consent

AIDS, acquired immunodeficiency syndrome; AMD, age-related macular degeneration; HIV, human immunodeficiency virus.

12-month follow-up visits. Fluorescein angiograms were obtained at baseline, 3 months, and 12 months. The fundus photographs and fluorescein angiograms were assessed at the UCLA Jules Stein Eye Institute Clinical Research Center Fundus Photograph Reading Unit (Los Angeles, California), where objective evaluations of the photographs and fluorescein angiograms were documented in a masked fashion. The Reading Unit was tasked with documenting all gross morphologic changes that occurred from baseline through completion with regard to (a) drusen size, character, and distribution, (b) development and progression of choroidal neovascularization, and (c) other interval fundus changes or abnormalities. The data from the reading center did not affect enrollment. Enrollment was based solely upon the determination of meeting eligibility criteria by the enrolling center ophthalmologist and its study coordinator.

TREATMENT PROTOCOLS FOR MIRA-1 STUDY

Qualified consenting patients aged 50 to 85 were randomly assigned to one of two treatment arms—the rheopheresis treatment group or the placebo-control group—in a 2:1 ratio, respectively. Oral supplementation consisting of zinc and high-dose vitamins and antioxidants was given to all enrolled patients. Depending on the randomization, each patient was scheduled to receive either eight rheopheresis or eight placebo procedures in a pulsed protocol delivered over a 10-week treatment period. In addition, any patient from either group who experienced a prospectively determined "improvement" at the 3-month postbaseline evaluation but then later showed a prospectively determined decrease at the 9-month postbaseline interval was eligible to receive two additional treatments (either rheopheresis or placebo) 2 weeks after the 9-month postbaseline visit. All patients were shrouded from the neck down to prevent them from determining their randomization arm (see "Masking Procedure" section).

Rheopheresis is not typically performed by a physician. In this study, medical technicians or nurses operating with indirect apheresis physician supervision provided all treatments. Rheopheresis treatments were administered in paired sessions, which treated one plasma volume per session with a 2-day recovery interval between each treatment session. Each treatment session required 2 to 4 hours to complete one plasma volume procedure, depending on the patient's size and the adequacy of venous access. Patients were continuously monitored during the treatment procedures with electrocardiography, automated blood pressure measurements, oxygen saturation monitoring, and intratreatment coagulation tests. A 16-day (±2 days) interval of "therapeutic rest" was provided between each of the paired treatment sessions. Placebo-control treatments were administered on a similar schedule but incorporated 2-hour masked sham procedures. These consisted of bilateral insertions of 21-gauge HepLok needles into the antecubital fossas of the patients. Adverse events and visual acuity were evaluated midway through the 10-week treatment period (before treatment 5) and at each of the 3-, 6-, 9-, and 12-month postbaseline follow-up intervals.

Rheopheresis Blood Filtration

Rheopheresis is a form of therapeutic plasma apheresis that utilizes a novel nanopore, hollow-fiber, membrane technology configured in a differential filtration array with two single-use, in-line, membrane filters. The process is designed to deplete excess concentrations of soluble high-molecular-weight plasma components by mechanically sieving from the blood circulating species larger than 25 nm (as measured across their shortest linear axis), or approximately 500 kDa by weight. The therapy results in the depletion of a size range of plasma components, including immune complexes, IgM, beta$_2$-macroglobulin, fibrinogen, von Willebrand factor, low-density lipoprotein cholesterol, and others.

Rheopheresis patients required bilateral insertions of 16-, 17-, or 18-gauge needles into each antecubital vein, connected to a single-use, sterile, closed-circuit, PVC tubing set. The Plasmatic (Kimal Scientific Products, Ltd, Rucorn, United Kingdom) or the OctoNova (Mesys GmbH, Hanover, Germany) blood pump provided blood circulation. The two-stage filtration process was provided by (a) the polyethylene plasma separator (Plasmaflo 0P-05W[L]) connected in series to (b) the plasma component separator (Rheofilter AR-2000), both manufactured by Asahi- Kasei Medical Co, Ltd (Tokyo, Japan).

Unlike conventional single-channel filtration plasma exchange, this membrane differential filtration system uses a dual-channel pumping mechanism designed to minimize hemolysis by continuously separating native whole blood into its plasma and cellular components with the plasma separation in a low-pressure circuit. In a separate pressurized circuit, the plasma is driven through the plasma component separation that sieves the plasma fraction, removing large (≥25 nm), soluble, high-molecular-weight components. The sieved plasma is then recombined with the cellular fraction in a heated reservoir, and the treated whole-blood mix is reinfused into the patient's opposite antecubital fossa via the sterile closed circuit. In this euvolemic process, no more than 600 mL of blood is circulating within the continuously heparinized extracorporeal system at any one time. Of note, no replacement fluids are required, and therefore the patient is not exposed to any allogeneic blood products. In addition, only heparin is given. No other medications are needed, and no sedation is required.

Randomization Procedure for MIRA-1 Study

Treatment nurses used sequentially numbered sealed envelopes containing computer-generated random number assignments to assign the treatment arm (rheopheresis vs placebo) at the time of the initial treatment. With respect to eyes, if both of a patient's eyes qualified, one eye was similarly randomized into the Primary (study) Eye Cohort by the clinical coordinator. Because multiple treatments were required, patients had to have been able to complete at least 75% of the initial plasma volume treatment in order to be considered an "intent-to-treat" patient. If a patient was assigned to rheopheresis treatment but failed to complete the first treatment owing to inadequate bilateral venous access, the patient was removed from the study and replaced using prespecified protocol procedures.

Masking Procedure

All patients were covered with an opaque shroud from the neck down prior to initiation of each treatment in order to mask them from observing their treatment. Additionally, their arms were covered with drapes throughout the process. A partition was positioned in front of the blood pump and plasma therapy system so that the patient could not view the system. The pump was activated regardless of treatment arm assignment so that in each case, the patient heard the background noise of the powered machine. Patients randomized to the placebo arm of the study received masked venipunctures with 21-gauge HepLok needles in both arms without connection to the tubing circuit. Placebo patients then underwent a 2-hour sham procedure, complete with frequent machine alarms

and checking of intravenous tube position. Ophthalmologic investigators were masked, because treatments were performed at separate locations, and the treatment personnel were prohibited from discussing treatment arm assignments with the ophthalmic investigators. Physicians did not have access to study treatment envelopes, treatment forms, or the randomization log, all of which were maintained in separate areas in locked files.

Data Management

Data acquisition was managed under a protocol developed with specific prospective guidance by the FDA. Data were collected directly from the study sites by a third-party clinical research organization, Promedica International (PMI, Huntington Beach, California), which had been retained from inception to provide independent, third-party, study-wide monitoring, data auditing, and database development services. A direct, secure data transfer of the pertinent variables was made from PMI to BioStat International (BI, Tampa, Florida), which was retained specifically to perform statistical evaluation of the ophthalmic data. PMI and BI do not have any relation to the study's sponsors, nor do they have any financial interests in the study's outcome. Data was then transferred to the authors by the Chief Operating Officer of Oculogix. The company was not involved in the writing of this article, and the company may use the data and other data not given to us to write a different article.

STATISTICAL ANALYSIS AND METHODS

Sample Size and Power

The statistical plan for the MIRA-1 trial was based on the results of the precedent German studies.[2] This sample size was expected to detect a difference with 95% to 98% power (two-sided test, alpha = .05) for the primary end point—comparison of mean line change in ETDRS (logMAR) BCVA. The null hypothesis was no difference in logMAR visual acuity from baseline in the rheopheresis treatment group relative to the placebo-control group. With the expected power of this study, the original intent of the interim analysis was (1) to demonstrate gross trends in efficacy outcomes without anticipation of statistical significance and (2) to evaluate safety parameters and reporting procedures.

Baseline Demographics

Demographic and baseline characteristics were summarized and tested for treatment group comparability using a Fisher exact test or chi-square test for categorical values. A Wilcoxon rank sum test was used to compare continuous variables.

Analytical Model: Analysis of Variance With Repeated Measures Analysis

Similar to the method used by the Age-Related Eye Disease Study (AREDS) trial, MIRA-1's end points (ie, mean changes in ETDRS [logMAR] visual acuity from baseline through the available post-treatment interval visits) were compared using two-group ANOVA with repeated measures analysis with unstructured covariance using SAS/STAT Software (SAS Institute Inc, Cary, North Carolina). Both the group effect (rheopheresis treatment vs placebo-control efficacy) and time effect (determines if relative logMAR acuity changes observed between rheopheresis treatment and placebo control are constant or change during the course of the study) were tested.

Proportions Analysis

Frequency distribution of changes in ETDRS BCVA from baseline using various threshold categories (≥2-line improvement, ≥3-line improvement, ≥2-line loss, ≥-3 line loss) were presented without inferential statistics because of the inevitable loss of power when converting continuous variables into binary responses in the context of the small sample size of the interim analysis group.

Visual Acuity Analysis

The primary end point for the study was prospectively identified as the comparison of mean change in logMAR BCVA in the designated primary (study) eyes cohort.

Intent-to-Treat Analysis

The primary visual acuity analyses were based on a strict intent-to-treat analysis; patients were analyzed within the group to which they were randomly assigned. The main analysis was performed comparing the primary (study) eyes cohort of the rheopheresis treatment group vs the placebo-control group.

Adverse Events

As is required of all FDA trials, adverse events were evaluated by documenting evidence of any and all adverse events that occurred over the course of the study. For each adverse event occurrence, the following were recorded: (a) date of onset, (b) date of resolution, (c) severity, (d) determination as to whether the event was treatment-related or non-treatment- related, (e) determination as to whether the event was serious or not serious, (f) action or treatment required, and (g) the outcome. Serious adverse events were considered to be those that required hospitalizations or administration of additional medical therapies. Anticipated treatment-related safety events included observations for episodes of dysrhythmias, hypotension, dizziness, paresthesias, flushing, nausea, vomiting, edema, lethargy, fatigue, chills, and hypoglycemia, among others.

Hematology Outcome Measures

All consenting patients submitted to baseline HIV and hepatitis antigen-antibody screening. Postenrollment blood samples were collected for complete blood cell count, blood chemistry, prothrombin time, partial thromboplastin time, lipid profile, fibrinogen, immunoglobulin levels, and select hemorheologic factors ($beta_2$-macroglobulin, serum and whole-blood viscosity) at baseline, each

pretreatment, each post-treatment, and at 3- and 6-month postbaseline follow-up intervals. Baseline laboratory measurements were compared between the rheopheresis treatment and placebo-control groups using *t* tests except for several variables that were analyzed by nonparametric Mann-Whitney tests due to skewness in the data.

Anatomic Outcome Measures

With regard to the detection of gross anatomic treatment effects (ie, a decrease in drusen or development of choroidal neovascularization), given a significance level of .05 and a treatment difference of possibly 15% between the treatment and placebo-control groups, the sample size of the interim analysis population provided only an 11% power to detect a significant difference in this secondary outcome at this juncture.

RESULTS

A total of 216 patients were randomized. Of these, 18 were not included in the adverse events or visual acuity evaluation because they did not complete one treatment. This, therefore, decreased the number of patients that were evaluated for safety concerns to 198 patients, 129 in the rheopheresis group and 69 in the placebo control group (Table 2). A further 15 were excluded from the intent-to-treat analysis—13 patients because of poor venous access and two patients that did not have one postbaseline efficacy measurement—leaving a total of 183 patients that had met the criteria for the efficacy analysis (Table 3). This included 69 of the placebo control and 114 of the rheopheresis-treated group. In the adverse events table (Table 4), the entire group of 198, even those that could not receive a treatment because of poor venous access, was included.

TABLE 2. BASELINE DEMOGRAPHICS OF THE ADVERSE EVENTS ANALYSIS GROUPS DURING MIRA-1 STUDY

CATEGORY		RHEOPHERESIS (N=129)	PLACEBO (N= 69)
Age (yr)			
Mean (SD)		75.0 (6.51)	74.2 (5.79)
Median		75.9	74.5
Minimum, maximum		56.0, 85.5	54.5, 86.0
<60	n (%)	2 (1.6)	1 (1.4)
60 to <70	n (%)	27 (20.9)	15 (21.7)
70 to <80	n (%)	71 (55.0)	42 (60.9)
≥80	n (%)	29 (22.5)	11 (15.9)
Weight (lb)			
Mean (SD)		176 (45.6)	173 (37.8)
Median		165	172
Minimum, maximum		104, 418	109, 263
Gender			
Male	n (%)	62 (48.1)	36 (52.2)
Female	n (%)	67 (51.9)	33 (47.8)
Race			
Caucasian	n (%)	124 (96.1)	69 (100.0)
Black	n (%)	0 (0.0)	0 (0.0)
Asian	n (%)	2 (1.6)	0 (0.0)
Hispanic	n (%)	3 (2.3)	0 (0.0)
Other	n (%)	0 (0.0)	0 (0.0)
Primary eye			
Right	n (%)	57 (44.2)	30 (43.5)
Left	n (%)	71 (55.0)	39 (56.5)

BASELINE DEMOGRAPHICS OF MIRA-1 STUDY

Demographic and baseline characteristics were summarized and tested for treatment group comparability using a Fisher exact test or chi-square test for categorical values. A Wilcoxon rank sum test was used to compare continuous variables (Tables 2, 3, and 5). The

mean age of the treated patients and the control patients in the adverse events analysis was 75 ± 6.5 years for the treated group and 74.2 ± 5.8 years for the control group (Table 2). For the visual acuity analysis, the mean age was 74.7 ± 6.68 and 74.2 ± 5.79 years, respectively (Table 3). There were 51.8% males in the treated group and 52.2% in the control group in the visual acuity analysis. The mean logMAR ETDRS at baseline was −0.4 ± 0.16 in the treated group and the same in the control (*P* = .9533) (Table 5).

TABLE 3. DEMOGRAPHICS OF THE ENTIRE VISUAL ACUITY INTENT-TO-TREAT GROUPS AND THE MODIFIED GROUPS IN THE MIRA-1 STUDY

CATEGORY		INTENT-TO-TREAT POPULATION		MODIFIED PER PROTOCOL POPULATION	
		RHEOPHERESIS (N=114)	PLACEBO (N= 69)	RHEOPHERESIS (N= 72)	PLACEBO (N= 49)
Age (yr)					
Mean (SD)		74.7 (6.68)	74.2 (5.79)	74.1 (6.32)	73.7 (6.21)
Median		74.9	74.5	74.3	74.2
Minimum, maximum		56.0, 85.5	54.5, 86.0	59.2, 85.1	54.5, 86.0
<60	n (%)	2 (1.8)	1 (1.4)	1 (1.4)	1 (2.0)
60 to <70	n (%)	25 (21.9)	15 (21.7)	17 (23.6)	12 (24.5)
70 to <80	n (%)	60 (52.6)	42 (60.9)	40 (55.6)	28 (57.1)
≥80	n (%)	27 (23.7)	11 (15.9)	14 (19.4)	8 (16.3)
Weight (lb)					
Mean (SD)		177 (46.5)	173 (37.8)	179 (47.7)	173 (39.2)
Median		168	172	170	175
Minimum, maximum		104, 418	109, 263	104, 418	109, 260
Gender					
Male	n (%)	59 (51.8)	36 (52.2)	41 (56.9)	24 (49.0)
Female	n (%)	55 (48.2)	33 (47.8)	31 (43.1)	25 (51.0)

ADVERSE EVENTS DURING MIRA-1 STUDY

Overall, in the treated group, 24.0% had an incident that required an intervention during the day of treatment compared to 5.8% of the controls. During the treatment phase, but not on the treatment day, 21.7% of the controls compared to 15.1% of the treated patients had an event that required an intervention. After the treatment phase, 34.4% of the treated patients and 27.5% of the control patients had an adverse event that required intervention (Table 4).

Of the 198 patients that had at least one treatment, there were 27 serious adverse events, but only 1.8% of treatments were suspended on account of adverse events. One patient developed bigeminy and one patient had possible angina on the day of treatment, but these events were felt to be unlikely related to treatment. One patient developed pneumonia during the treatment phase. During the post-treatment phase, one developed atrial fibrillation; 23 other adverse events occurred during this phase that were not associated with the treatment (Table 6).

VISUAL ACUITY RESULTS OF MIRA-1 STUDY

A total of 179 patients had vision evaluation at 3 months. Of these, 111 patients had undergone rheopheresis and 68 were controls. The mean logMAR line change for the treated patients was 0.07 ± 0.138 and for the placebo group was 0.07 ± 0.160. This was not statistically significant (*P* = .8633). At 12 months, there were 104 treated patients and 63 placebo patients that had follow-up. The treated patients had a LogMAR vision of 0.02 ± 0.213, and the placebo patients, 0.02 ± 0.20. This was not statistically significant (*P* = .977). Vision measurements at 6 and at 9 months were not statistically different between the control and the treated patients (Table 7). The repeated measure *P* value for the entire time interval was not significant (*P* = .69).

TABLE 4. ADVERSE EVENTS DURING THE MIRA-1 STUDY

STUDY PHASE	CATEGORY	RHEOPHERESIS N (%)	PLACEBO N (%)	ALL SUBJECTS N (%)
Subject incidence*				
On the day of treatment	N	129	69	198
	All events	50 (38.8)	9 (13.0)	59 (29.8)
	Requiring intervention	31 (24.0)	4 (5.8)	35 (17.7)
	Resulting in treatment suspension	12 (9.3)	2 (2.9)	14 (7.1)
During the treatment phase but not on the day of treatment	N	126	69	195
	All events	19 (15.1)	15 (21.7)	34 (17.4)
	Requiring intervention	9 (7.1)	11 (15.9)	20 (10.3)
	Resulting in study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
After the treatment phase	N	122	69	191
	All events	42 (34.4)	19 (27.5)	61 (31.9)
	Requiring intervention	37 (30.3)	19 (27.5)	56 (29.3)
	Resulting in study discontination	0 (0.0)	0 (0.0)	0 (0.0)
Treatment incidence†				
On the day of treatment	N	900	551	1451
	All events	86 (9.6)	12 (2.2)	98 (6.8)
	Requiring intervention	44 (4.9)	4 (0.7)	48 (3.3)
	Resulting in treatment suspension	16 (1.8)	4 (0.7)	20 (1.4)

*Number of subjects with at least one report. Percentage based on number of subjects in the safety population available in that interval.
†Number of treatments with at least one report. Percentage based on number of treatments in the safety population.

TABLE 5. BASELINE BEST-CORRECTED VISUAL ACUITY IN THE INTENT-TO-TREAT GROUP AND THE MODIFIED PER-PROTOCOL GROUP IN THE MIRA-1 STUDY

BCVA	INTENT-TO-TREAT POPULATION			MODIFIED PER-PROTOCOL POPULATION			*P* VALUE*
	RHEOPHERESIS (N=114)	PLACEBO (N= 69)	TOTAL (N=183)	RHEOPHERESIS (N= 72)	PLACEBO (N= 49)	TOTAL (N=121)	
EDTRS logMAR							
Mean (SD)	-0.40 (0.16)	-0.40 (0.16)	-0.40 (0.16)	-0.38 (0.14)	-0.37 (0.16)	-0.38 (0.14)	
Median	-0.38	-0.38	-0.38	-0.37	-0.34	-0.36	
Min, Max	-0.92 , -0.12	-0.80 , -0.18	-0.92 , -0.12	-0.76 , -0.16	-0.80 , -0.18	-0.80 , -0.16	
P value†	0.9533			0.7327			.2318
20/20 or better n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
20/25 or better n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
20/32 or better n (%)	5 (4.4)	5 (7.2)	10 (5.5)	3 (4.2)	5 (10.2)	8 (6.6)	
20/40 or better n (%)	38 (33.3)	27 (39.1)	65 (35.5)	25 (34.7)	23 (46.9)	48 (39.7)	
20/80 or better n (%)	101 (88.6)	59 (85.5)	160 (87.4)	68 (94.4)	43 (87.8)	111 (91.7)	
20/100 or better n (%)	108 (94.7)	67 (97.1)	175 (95.6)	71 (98.6)	48 (98.0)	119 (98.3)	

TABLE 5 (CONTINUED). BASELINE BEST-CORRECTED VISUAL ACUITY IN THE INTENT-TO-TREAT GROUP AND THE MODIFIED PER-PROTOCOL GROUP IN THE MIRA-1 STUDY

BCVA	INTENT-TO-TREAT POPULATION			MODIFIED PER-PROTOCOL POPULATION			*P* VALUE*
	RHEOPHERESIS (N=114)	PLACEBO (N= 69)	TOTAL (N=183)	RHEOPHERESIS (N= 72)	PLACEBO (N= 49)	TOTAL (N=121)	
20/125 or better n (%)	111 (97.4)	69 (100.0)	180 (98.4)	72 (100.0)	49 (100.0)	121 (100.0)	
Worse than 20/125 n (%)	2 (1.8)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	
20/200 or worse n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Not reported N	1	0	1	0	0	0	

BCVA, best-corrected visual acuity.
*Comparisons of total between populations using a *t* test.
†Comparison of treatment groups within populations using a *t* test.

In conclusion, there was no apparent significant difference between the two groups in the intent-to-treat analysis. Further analysis of the data was performed. There appeared to have been patients entered into both arms of the study that did not meet inclusion criteria, and eight patients had only four rheopheresis treatments. A total of 37% of the treated patients and 29% of the placebo data was then excluded from the analysis, and at that point there appeared to be a statistically significant difference between the treated patients and the control patients at 1 year with a *P* value of .001 (repeated measures *P* value =.01). In this subgroup, labeled as the "modified per protocol" group, the treated patients improved the logMAR lines of vision by 0.08 ± ± 0.166 compared to the control placebo group that decreased the logMAR lines of vision by –0.01 ± 0.164 (Tables 3, 4, and 8).

TABLE 6. SERIOUS ADVERSE EVENTS DURING THE MIRA-1 STUDY

RELATION TO TREATMENT	TREATMENT DAY	TREATMENT PHASE	POST-TREATMENT
Possible			Atrial fibrillation (1)
Unlikely	Bigeminy (1)	Pneumonia (1)	Other (4)
	Possible angina (1)		
Not Related			Other (19)

TABLE 7. VISUAL ACUITY RESULTS IN THE TREATED AND CONTROL GROUPS AT FOLLOW-UP OF THE MIRA-1 STUDY

SUBSET DESCRIPTION	3 MONTHS		6 MONTHS		9 MONTHS		12 MONTHS		REPEATED MEASURES *P* VALUE
	RHEO	PLACEBO	RHEO	PLACEBO	RHEO	PLACEBO	RHEO	PLACEBO	
Intent-to-treat population									
N	111	68	104	65	97	65	104	63	
Mean	0.07	0.07	0.05	0.03	0.04	0.03	0.02	0.02	
SD	0.13	0.160	0.164	0.194	0.21	0.173	0.213	0.20	
P value (ANCOVA)		.863		.561		.897		.977	.6937

Rheo = rhopheresis.

TABLE 8. MODIFIED GROUP ANALYSIS OF THE MIRA-1 STUDY

SUBSET DESCRIPTION	3 MONTHS		6 MONTHS		9 MONTHS		12 MONTHS		REPEATED MEASURES *P* VALUE
	RHEO	PLACEBO	RHEO	PLACEBO	RHEO	PLACEBO	RHEO	PLACEBO	
Modified per protocol									
N	72	48	68	48	65	47	68	45	0.0099
Mean	0.09	0.06	0.09	0.01	0.08	0.03	0.08	-0.01	
SD	0.129	0.142	0.134	0.197	0.174	0.136	0.166	0.164	
P value (ANCOVA)		.314		.004		.152		.001	

Rheo = rheopheresis.

DISCUSSION

MIRA-1 is the largest double-masked apheresis trial ever undertaken and is the largest prospective trial to evaluate the use of an extracorporeal therapy for an ophthalmic disease. Specifically, MIRA-1 is the first multicenter, prospective, randomized, double-masked, placebo-controlled study designed to investigate patients with nonexudative AMD.

The preliminary analysis of the final results of the MIRA-1 trial, which was to be the pivotal trial for rheopheresis, did not show a difference in the intent-to-treat group compared to controls at 1 year. If one segregates out post hoc the patients who failed to meet study inclusion criteria and should not have been enrolled by the participating ophthalmologist, as well as another eight patients that had fewer than four treatments, there appears to have been an effect. Unfortunately, this would be an exclusion of 37% of the treatment patients and 29% of the placebo patients. In addition, this excludes patients thought, by the recruiting ophthalmologist, to have pigment epithelial detachments that met this vague inclusion criteria (Table 1) but that in post hoc analysis may not have. Two possibilities exist, the first one being that rheopheresis, at least in the method that was used, does not work in patients with nonexudative AMD. It is possible that the number of treatments used in this trial was insufficient to produce the rheologic alterations necessary to improve vision. In the Utah trial, a smaller pilot study involving 30 patients (10 treated, 10 sham procedure, 10 control), a benefit of rheopheresis was identified among patients receiving 10 treatments over 20 weeks (Swartz M, Rabetoy G. Treatment of non-exudative age-related macular degeneration using membrane differential filtration apheresis. *Invest Ophthalmol Vis Sci* 1999;40:S319 [abstract]). In the MAC trial, which involved 40 patients (20 treated with rheopheresis and 20 controls), five treatments over 21 weeks were found to be effective.[2] This could help to explain why removal of the four patients that had only four or fewer rheopheresis treatments improved the results. It may be, as seen in the MAC trial, that a minimum number of treatments is necessary to produce an effect.[2]

A second possibility is that poor patient selection may have been responsible for the absence of an identifiable treatment effect. Selection of patients was left to the ophthalmologist as long as certain rheologic criteria and vision criteria were met. Unfortunately, some of those characteristics were not met on reevaluation of the fundus findings. In addition, the acceptance of patients with geographic atrophy and pigment epithelial detachments could have confounded the results. It is possible that those with pigment epithelial detachment actually had underlying choroidal neovascular membrane, and indocyanine green angiography and optical coherence tomography (OCT) were not required to ascertain that there was evidence of a choroidal neovascular membrane. The use of OCT now helps to determine the presence of subretinal fluid, which helps to determine if there is a choroidal neovascular membrane.

The interim analysis on the first third of cases appeared to show some effect in the treatment group.[1] In addition, it did not show evidence of a marked incidence of serious adverse events, which resulted in FDA approval of continuation of the trial. The data was reevaluated to determine if there were patients in either group that failed to meet inclusion criteria, and even afterwards, the data still showed a statistically significant beneficial effect ($P < .01$). Considering the final results, careful evaluation of the initial third may show that there was no effect in that group as well. Alternatively, it could have been possible that the investigators were more scrupulous about entering patients in the first third of the study than in the later two thirds. Regardless, the data appears flawed and so a well controlled and monitored randomized trial should be performed.

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PEER DISCUSSION

DR STEPHEN S. FEMAN: Everyone interested in retinal disorders has been waiting for these results. Other studies, such as the AREDS trials, may help prevent the progression of dry, atrophic-appearing, age related macular degeneration. However, there are few investigations of methods to reverse this disorder at this early stage. Rheopheresis may be the way of the future. If the scientific theory behind the MIRA-1 Trial is correct, it may be possible to shrink drusen, flatten RPE detachments, and reverse the earliest changes of age related macular degeneration. If that is done, it should be possible to prevent vision loss in this blinding disorder.

The preliminary data from the first 43 patients enrolled in this study was presented at our 2002 meeting.[1] At that time the treated eyes averaged 1.6 lines of improvement with LogMAR testing (P=.0011), and 13% of those eyes were able to see an additional 3 or more lines on the eye chart. Surprisingly the preliminary data found that eyes with poorer vision (20/40 or worse) seemed to do better than eyes with better vision (P=.0014). That report was used to show that a statistically valid study could be completed with 150 patients. With that as a guide it was possible to finish enrollment in 2004, and complete all of the patient study exams in 2005. Now it is seen that 216 patients were involved in the study and 12-month follow-up data is available for 167. Therefore, today's report should be definitive.

Since the 2002 AOS meeting, additional information has become available in the non-peer reviewed literature and at several websites.[2-4] In February of 2006 it was indicated that Phase III showed no differences between the treated and the control groups. The reports indicated that treatment did not cause a statistically significant difference in the best corrected visual acuities when measured at the 12-month exam. Afterwards a more detailed sub-group analysis was initiated.[3,4]. This found a mean vision gain of 0.8 lines in the treated group and a mean vision loss of 0.1 lines in the placebo group (P=.0147) at 12-months. In addition, 50% of the treated patients that started with vision poorer than 20/40, could see 20/40 or better at 12 months, while this happened in only 20% of the eyes of patients treated with the placebo. As a result many continue to believe a treatment benefit exists but the results require a finer measurement.

Now we have much more data. Sadly, there are more problems than expected. In the group that completed at least one treatment, 27 (16%) had serious adverse events that required medical therapy. In addition, if all the data is examined, it is found that 216 patients were enrolled initially, and 32 dropped out before completing the first treatment session. If all the data is combined to include every one of the 216 patients, many disturbing features are noted. The first was just described, 59 (27%) of the enrollees dropped out of the study or had serious complications. On top of that are significant factors that harm the science of this study. The data reveals that inappropriate patients were entered into both arms of the study. Subgroup analysis required removal of all data regarding those patients. That is, all of the data from 37% of the treated patients and 29% of those that received placebo therapy had to be deleted before subgroup analysis. As a result, the one-year sample size in this report is 110 patients, when a minimum of 150 patients was needed. For this reason, this study is incomplete.

As mentioned, the concept of using rheopheresis to treat the early stages of age related macular degeneration makes great sense. It should work, but we have yet to learn how to do this. Unfortunately, today's presentation appears to give us two conclusions:. this study was flawed and cannot be interpreted and there is insufficient data to show a treatment benefit. Nevertheless, this remains a reasonable theoretical concept.

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DR ALLAN J. FLACH: Risk benefit is where it's at with all therapies. You mentioned a 24 % intervention rate and a 27 % serious adverse rate. What exactly were the reasons for the interventions? What exactly were the adverse events? What were the reasons for the 32 dropouts, which seriously affects the significance of this study?

DR FREDERICK L. FERRIS: I share your concern about sub-group analyses. To see how easily one can get fallacious conclusions from subgroup analyses, one only has to look at sub-group analyses where you divide by astrological sign for example and find a statistically significant result for the Taurus's and the Libras, but not for the rest of the group. A more serious issue is that there are approximately 8 million people in this country who potentially would be eligible for this treatment, and it is both expensive and has some serious risks associated with the treatment. Could you comment on the whether the value of this research, which over the years has shown some consistency at least across studies, is enough to make one hope that there may be an effect of changing these serum lipids or immunoglobulins in a way that would be helpful. I wonder if the value of this research might be more in providing additional evidence that we ought to be thinking of other approaches to lowering the serum levels of these compounds than filtering the blood, which may be dangerous.

DR ROBERT C. DREWS: I was also concerned with the cost, especially considering the large number of people.

DR RICHARD C. TROUTMAN: Have the risk factors that you mentioned been eliminated in all these patients or were they eliminated during the study in the individual patients?

DR EDWIN M. STONE: I wonder what you think about an Apo A-I Milano sort of treatment. That is, an endogenous biological rheophoresis as opposed to a mechanical one?

DR JOSE S.PULIDO: Some questions are really asking "Is this allopathic treatment of a homeopathic medicine?" In other words, could greater use of the rheophoresis actually work? It does for familial hypercholesterolemia where it decreases the chance of cardiac disease and death from cardiac disease. Is this homeopathic use of an allopathic medicine? Would one need more treatments than just eight in one year?

The adverse events are listed in the paper. There were some serious adverse events, including one patient that developed atrial fibrillation, one patient developing bigeminy, and one patient developing pneumonia. That is not a huge number, but adverse events do occur. In terms of what were interventions required, it was that the blood pressure dropped or the patient became hypoglycemic during the treatment, and therefore required glucose or IV saline. So interventions are sometimes needed.

There is speculation as to whether this procedure works and whether other treatments may be more reasonable. Apo A-I Milano is a really fascinating story. There is a small group of people that live in a little town outside of Milan. These people smoke and eat whatever they want, and they do not die of heart disease. They have a mutation in one of their Apo lipoproteins that allows them to remove cholesterol from their vascular system. There is a company in Ann Arbor that has made recombinant Apo Milano, and it is presently in trials for cardiovascular disease. That could that be another way of doing rheophoresis without putting a patient on the machine. But until that becomes available well-run academic center trials, such as ours, seem reasonable