MULTICENTER PROSPECTIVE, RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED STUDY OF RHEOPHERESIS TO TREAT NONEXUDATIVE AGE-RELATED MACULAR DEGENERATION: INTERIM ANALYSIS

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ABSTRACT

Objective: To evaluate the safety and efficacy of Rheopheresis blood filtration to treat intermediate- to late-stage preangiogenic age-related macular degeneration (AMD) with soft drusen.

Design: Multicenter, prospective, randomized, double-masked, placebo-controlled clinical trial.

Participants: First 43 randomized patients (28 Rheopheresis and 15 placebo-control patients) with available baseline and 3-month postbaseline best corrected visual acuity (BCVA) measurements and intermediate- to late-stage preangiogenic AMD with multiple large soft drusen and elevated serum levels of targeted macromolecules.

Intervention: Patients were randomly assigned to receive eight Rheopheresis or eight placebo procedures over 10 weeks.

Main Outcome Measures: ETDRS BCVA measurements at baseline, 3, 6, 9, and 12 months postbaseline.

Results: In primary eyes, the mean LogMAR line difference between Rheopheresis and placebo-control eyes was 1.6 lines at 12 months postbaseline; the difference was significant throughout the first posttreatment year (P = .0011, repeated measures analysis). Thirteen percent of Rheopheresis compared with 0% of placebo-control eyes had a ≥3-line improvement in BCVA at 12 months postbaseline. Four percent of Rheopheresis compared with 18% of placebo-control eyes had a ≥3-line loss in BCVA.

The subgroup of patients whose primary eyes had baseline BCVA worse than 20/40 demonstrated a mean LogMAR difference between Rheopheresis and placebo-control eyes equaling 3.0 lines at 12 months postbaseline; the difference was significant throughout the first posttreatment year (P = .0014, repeated measures analysis). Sixteen percent of Rheopheresis compared with 0% of the placebo-control eyes had a ≥3-line improvement in BCVA at 12 months postbaseline. Five percent of Rheopheresis compared with 29% of placebo-control eyes had a ≥3-line loss in BCVA. Fifty-eight percent of Rheopheresis eyes improved to 20/40 or better, compared with 14% of placebo-control eyes. No serious treatment-related adverse events were observed.

Conclusions: Rheopheresis demonstrated statistically significant and clinically relevant effects on BCVA when compared with placebo controls for the 12-month study interval. Untreated patients with BCVA worse than 20/40 with intermediate- to late-stage preangiogenic AMD, soft drusen, and elevated blood factors were at risk for substantial visual loss. A sample size larger than 43 patients is important to provide a basis for widespread adoption of novel therapeutic options for AMD such as Rheopheresis. Therefore, enrollment to 150 patients is continuing.

Trans Am Ophthalmol Soc 2002;100:85-108

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of acquired legal blindness and visual impairment among people older than 50 years in the United States and other Western industrialized societies.[1-3] According to the National Eye Institute, AMD severely impairs the vision of 1.7 million Americans older than age 60. The risk of a person older than 75 developing the disease approaches 30%, and as the population ages, the number of AMD cases with severe visual loss is expected to rise to 6.3 million by 2020 if current population growth trends

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continue. New modalities of treatment are therefore needed to prevent loss of vision in the affected population.

Preangiogenic (nonexudative, or "dry") AMD is the most common form of the disease, representing up to 90% of the affected population. The only treatment to date that has demonstrated any positive effect on visual outcomes with this stage of AMD has been the use of zinc and high-dose antioxidants. Daily oral intake of these common dietary supplements has been shown to reduce progression to the more advanced stages of the disease, including "wet" AMD, by up to 25%.[4]

Approximately 80% of severe vision loss caused by AMD is due to the wet form of the disease. Patients whose eyes are characterized primarily by drusen in one or both eyes typically do not manifest a significant loss of vision. However, they are at an increased risk for progression to the later stages of the disease with a concomitant loss of significant visual acuity.[5] Risk factors for that development include number, size, and confluence of drusen and abnormal pigment clumping.[6] Patients with bilateral soft drusen have a 12.4% risk of exudative AMD developing within 10 years.[7] Patients with exudative AMD in one eye and soft drusen in the fellow eye represent a group at high risk of becoming legally blind.[6]

BACKGROUND

Over the last decade, a series of clinical trials in Germany and now the United States have evaluated the use of the Rheopheresis blood filtration technology for the treatment of AMD. The research began with several uncontrolled case series. Promising results provided the basis to initiate the first controlled randomized clinical trial to investigate the safety and efficacy of Rheopheresis in patients with AMD (the MAC-1 Trial) at the University of Cologne.[8-12] In each study, the Rheopheresis group consistently demonstrated statistically significant improvement in mean ETDRS (LogMAR) best corrected visual acuity (BCVA) that was sustained after the treatment period. Although many forms of AMD were evaluated at different stages of disease progression, eyes with multiple soft drusen and without evidence of neovascularization consistently demonstrated the best therapeutic results. In 1998, Swartz and colleagues (*Investigative Ophthalmology and Visual Science* 1999:40(4):5319) undertook a Food and Drug Administration (FDA) pilot study (IDE G970241) of 30 patients with preangiogenic AMD with soft drusen at the University of Utah. Its findings suggested that further study was warranted.

THE MIRA-1 TRIAL

The current MIRA-1 (**M**ulticenter **I**nvestigation of **R**heopheresis for **A**MD) study design expands on these preceding trials. MIRA-1 is a 12-month randomized, prospective, multicenter, double-masked, placebo-controlled, FDA clinical trial designed to compare Rheopheresis treatment with placebo-control treatment in 150 patients with intermediate- to late-stage (AREDS grade 3 to 4, BCVA between 20/32 and 20/125 inclusive), high-risk (≥10 large soft drusen), preangiogenic AMD who also demonstrate the elevation of serum levels of select hemorheologic macromolecules in their blood. As such, MIRA-1 is the largest prospective, double-masked apheresis trial ever undertaken. We report on the interim results of the initial group of 43 randomized, intent-to-treat patients.

From the FDA pilot trial conducted at the University of Utah, it was determined that fibrinogen, serum IgA, and total cholesterol, as rheologically relevant high-molecular-weight proteins, were highly associated with positive treatment outcomes and might prove useful in optimizing inclusion criteria within the setting of the MIRA-1 protocol. These findings are consistent with epidemiological studies that established cholesterol, fibrinogen, alpha$_2$-macroglobulin, vascular endothelial growth factor (VEGF), von Willebrand factor, and plasma viscosity as factors associated with AMD.[13-16]

PATIENTS AND METHODS

SITES

A total of nine 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 (CRO) ProMedica International (Huntington Beach, California).

PATIENT SELECTION AND ENTRY EVALUATIONS

The FDA has authorized up to 180 patients for enrollment with the goal of having at least 150 evaluable patients at the conclusion of the trial. 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 criteria for study eligibility are listed in Table I.

In addition, fundus photographs were obtained at baseline and at 3, 6, 9, and 12 months at 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.

TREATMENT PROTOCOLS

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. Of the 43 patients included in this interim analysis, only two

TABLE I: INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

Patients of any race between the ages of 50 and 85 yr 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.[2]
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 3 disc diameters within 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 2 of the following 3 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 prothombin (PT) and partial thomboplastintine (PTT) clotting times with the exception of patients who are stable on long-term coumadin therapy.
Patients must have adequate bilateral antecubital venous access.
Patient 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 k/μL.
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.

AMD, age-related macular degeneration.

received booster treatments (one patient received two treatments, while the other received one treatment). All patients were shrouded from the neck down to prevent them from determining their randomization arm (see "Masking Procedure"). Rheopheresis is not typically performed by a physician. In this study, medical technicians or nurses operating with indirect apheresis physician supervision provided all 343 treatments.

Rheopheresis treatments were administered in paired 100% plasma volume processing sessions with a 2-day recovery interval between each treatment session. Each treatment session required 2 to 4 hours to complete a 100% plasma volume processing procedure, depending on the patient's size and the adequacy of venous access. Patients were continuously monitored with ECG, automated blood pressure, oxygen saturation, 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 charades initiated with bilateral insertions of 21-gauge HepLok needles. Efficacy and safety parameters 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 (Figure 1). The process incorporates a protocol designed to deplete excess concentrations of soluble high-molecular-weight plasma components by mechanically sieving circulating species larger than 25 nm (as measured across their shortest linear axis) or approximately 500 kDa by weight from the blood. As such, the therapy provides physiologic depletions of a targeted bandwidth of plasma species, including immune complexes, IgM, α_2-macroglobulin, fibrinogen, Von Willenbrandt Factor, low-density lipoprotein cholesterol (LDL-C), and others.[17]

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 blood pump (Kimal Scientific Products, Ltd, Rucorn, United Kingdom) provided blood circulation. The two-stage filtration process was provided by (a) the plasma separator (Plasmaflo 0P-05W[L]) connected in series to (b) the plasma component separator (Rheofilter AR-2000), both manufactured by Asahi Medical Co, Ltd (Tokyo, Japan).

Unlike conventional single-channel plasma exchange, this membrane differential filtration (MDF) system uses a dual-channel pumping mechanism designed to minimize hemolysis by continuously separating native whole blood into its plasma and cellular components in a low-pressure circuit. In a separate pressurized circuit, the plasma is driven through the plasma component filter 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 enriched whole-blood mix is reinfused back into the patient 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, only autologous blood products are reintroduced into the patient's circulation. In addition, only heparin is given. No other medications are needed, and no sedation is required. Two investigational sites performed Rheopheresis treatments in segregated, converted storage rooms as in-office procedures. One site utilized their adjacent ophthalmic surgery center in conjunction with a mobile apheresis team. Six sites partnered with affiliated or nearby dialysis or blood centers to provide treatment.

RANDOMIZED PROCEDURE

Treatment nurses used sequentially numbered sealed envelopes containing computer-generated random number assignments to assign the treatment arm (Rheopheresis versus 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.

Since 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,

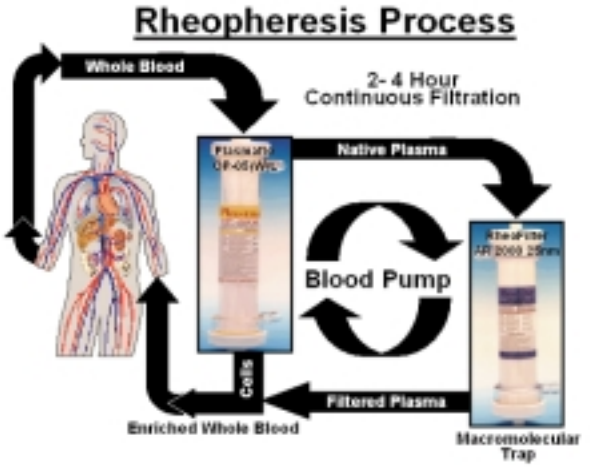

FIGURE 1
Rheopheresis blood filtration process.

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 initiating 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 needlesticks with 21-gauge HepLok needles in both arms without connection to the tubing circuit. Placebo patients then underwent a 2-hour charade, complete with frequent machine alarms and checking of intravenous tube positioning.

Ophthalmologic investigators were masked, since 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 guidance provided prospectively by the FDA. Data were collected directly from the study sites by a third-party CRO, 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.

In the interim analysis, 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 for this interim analysis. The study's affiliate sponsor, Apheresis Technologies Inc (Palm Harbor, Florida), provided BI with a sealed copy of the randomization code for the 43 interim analysis patients only. Burkhart and Associates (BA, Salt Lake City, Utah) provided safety analysis under a similar protocol. PMI, BI, and BA do not have any relation to the study's sponsors, nor do they have any financial interests in the study's outcome.

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.[8-10] The current study called for an analysis of 150 available patients randomized into either Rheopheresis treatment or placebo-control groups on a 2:1 ratio. This sample size was expected to detect a difference with 95% to 98% power (2-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: ANOVA 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 posttreatment 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 versus 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.

PROPROTIONS 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.

EFFICACY OUTCOME MEASURES

The primary efficacy end point for the study and this interim analysis was prospectively identified as the comparison of mean change in LogMAR BCVA in the designated primary (study) eyes cohort comparing the

Rheopheresis treatment group with the placebo-control group. The interim analysis evaluated all available BCVA data on the first 43 enrolled intent-to-treat patients from baseline to the last available postbaseline follow-up visit.

Secondary efficacy outcomes included proportions of eyes with ≥2-line (10 letters) or ≥3-line (15 letters) loss or gain of best corrected ETDRS acuity. In addition, the proportion of cases with baseline ETDRS BCVA worse than 20/40 that achieved 20/40 or better acuity posttreatment was also determined because of the functional significance of 20/40 vision as a legal threshold criterion for maintaining a valid driver's license.

INTENT-TO-TREAT ANALYSIS

The primary efficacy analyses were based on a strict intent-to-treat analysis; patients were analyzed within the group to which they were randomly assigned. All 43 patients that had available baseline and 2-week posttreatment (3-month postbaseline) LogMAR BCVA measures at the time of closeout of the interim analysis database were included. One patient received only five of the planned eight Rheopheresis treatments, while another patient received seven of the planned eight Rheopheresis treatments. Two patients received one and two Rheopheresis booster treatments, respectively. The same series was later updated to include available follow-up through the 12-month postbaseline interval. The analysis presented here represents a consecutive series of cases with the following exceptions:

Three patients randomized to the Rheopheresis group were replaced, as per the protocol, at the time of their initial treatment owing to an inability to obtain adequate bilateral venous access. Two additional patients were randomized within the same time frame of the 43-case interim analysis, but their 2-week posttreatment interval data were not available to PMI at the time the interim analysis data collection period was closed. These patients' data will be included in all subsequent analyses. One patient was enrolled without documentation of baseline LogMAR BCVA, and thus no BCVA efficacy analysis was possible.

The main analysis was performed comparing the primary (study) eyes cohort of the Rheopheresis treatment group versus the placebo-control group. Since treatments were systemic, analyses were also performed for the all-qualifying-eyes and all-eyes cohorts of the 43 cases, regardless of the qualification or visual status in the contralateral eye.

All cases that had baseline ETDRS BCVA worse than 20/40 were analyzed separately as a subset.

SAFETY OUTCOME MEASURES

As is required of all FDA trials, safety was 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. 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 (PT), partial thromboplastin time (PTT), lipid profile, fibrinogen, immunoglobulin levels, and select hemorrheologic factors (α_2-macroglobulin, serum and whole-blood viscosity) at baseline, each pretreatment, each posttreatment, 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

BASELINE DEMOGRAPHICS

There were 43 patients involved in the interim analysis: 28 Rheopheresis treatment and 15 placebo-control patients. Both eyes qualified for treatment based on the enrollment criteria in 11 (26%) of the enrolled patients.

The baseline characteristics of the Rheopheresis treatment and placebo-control groups with regard to age, sex, and mean baseline LogMAR acuity were not significantly different in the Rheopheresis treatment and placebo-control groups (Table II). The mean visual acuity was 20/47 for the Rheopheresis treatment group and 20/49 for the placebo-control group (P= .81). All patients in the Rheopheresis treatment and placebo-control

TABLE II: BASELINE PATIENT CHARACTERISTICS AND DEMOGRAPHICS

VARIABLE	TREATMENT	PLACEBO	*P* VALUE
Age (yr)			
Mean ± SD	74.8 ± 7.8	74.7 ± 5.9	.94
Median	76.5	74.0	
Range	59-85	66-85	
Distribution:			
<60	1 (4%)	0	
60-69	7 (25%	4 (27%)	
70-79	11 (39%)	8 (53%)	
80+	9 (32%)	3 (20%)	
Sex			
Male	16 (57%)	5 (33%)	.14
Female	12 (43%)	10 (67%)	
Mean LogMAR ± SD	0.37 ± 0.11	0.39 ± 0.17	.81
Mean visual acuity	20/47	20/49	

groups were Caucasian except one in the Rheopheresis treatment group, who was Asian.

Table III provides a listing of selected baseline laboratory values by treatment and placebo groups. With the exception of baseline serum uric acid level, which was significantly higher in the Rheopheresis treatment group than in the placebo-control group (5.24 mg/dL treatment versus 4.26 mg/dL placebo, $P = .01$), there were no significant differences at baseline between the Rheopheresis treatment and placebo-control groups in any other of the 62 blood parameters tested. Nine mean baseline laboratory values were elevated in both the Rheopheresis treatment and placebo-control groups (ie, fibrinogen, international normalized ratio [INR], PT, serum intracellular adhesion molecule-1 (sICAM-1), total cholesterol, very low-density cholesterol (VLDL-C), LDL-C, serum osmolality, and whole-blood viscosity). It appears likely that these hemorrheologic abnormalities were present on account of protocol enrollment criteria that specifically preselected and sought to qualify patients with elevated levels of certain high-molecular-weight blood components (see "Inclusion Criteria," Table I).

INTENT-TO-TREAT ANALYSIS

The results of the analysis of variance (ANOVA) repeated-measures analysis, as well as the mean LogMAR line difference between Rheopheresis treatment and placebo-control groups at the 12-month postbaseline interval, are shown in Table IV. In the Primary Eye cohort, the 12-month postbaseline mean LogMAR line difference between Rheopheresis treatment and placebo-control groups was 1.6 lines (group effect (GE) $P = .0011$). The time effect (TE) was not significant ($P = .2560$), indicating a "therapeutic plateau" (ie, there was no significant change in the therapeutic benefit of the Rheopheresis treatment group relative to the placebo-control group over the 12-month course of the trial). These results are graphically depicted in Figure 2. Similar findings were consistently observed in both the all-qualifying-eyes cohort (GE $P = .0053$ and TE $P = .2570$), and the all-eyes cohort (GE $P = 0.002$ and TE $P = .4093$) as well.

Table V demonstrates the proportional changes in LogMAR acuity at each of the postbaseline interval visits for the primary eyes cohort. The Rheopheresis treatment group consistently had a greater proportion of cases with line improvements at each postbaseline interval, compared with the placebo-control group, regardless of which threshold criterion (≥1 line, ≥1.5 lines, ≥2 lines, ≥2.5 lines or ≥3 lines) for BCVA, improvement was used. At 9 and 12 months postbaseline, 13% and 12% of the Rheopheresis treatment eyes had a ≥3-line improvement in BCVA respectively, compared with 0% and 0% of the eyes in the placebo-control group (Figure 3). Similarly, the Rheopheresis treatment group consistently had a smaller proportion of cases with BCVA line losses at each postbaseline interval compared with the placebo-control group (Table V). At 12 months postbaseline, only 4.0% of the Rheopheresis treatment eyes had a ≥3-line loss of BCVA compared with 18.2% of the eyes in the placebo-control group (Figure 4).

SUBGROUP ANALYSIS: EYES WITH BASELINE ETDRS BCVA WORSE THAN 20/40

In the subset of the primary eyes cohort with baseline LogMAR BCVA worse than 20/40, the mean 12-month postbaseline interval LogMAR line difference between Rheopheresis treatment and placebo-control groups was 3.0 lines (15 letters; GE $P = .0014$ and TE $P = .2928$). Figure 5 demonstrates that the mean line difference between the two groups tended to increase over time. This was largely due to the progressive loss of mean BCVA in the placebo-control eyes, while the posttreatment improvement in mean BCVA in the Rheopheresis-treated eyes remained essentially constant (1.3 lines posttreatment and 1.1 lines at the 12-month postbaseline interval). Again, the GE and TE outcomes were consistent in both the all-qualifying-eyes (GE $P = .0122$ and TE $P = .2747$) and the all-eyes (GE $P = .0050$ and TE $P = .3565$) cohorts as well.

In the subset of cases with baseline LogMAR BCVA worse than 20/40, the Rheopheresis treatment group consistently demonstrated a greater proportion of cases with ETDRS line improvements at each postbaseline interval compared with the placebo-control group (Table V). In fact, none of the placebo-control cases had a ≥3-line improvement in vision at any postbaseline interval, compared with 18.8% and 15.8% of the Rheopheresis treatment patients achieving this level of improvement at the 9- and 12-month postbaseline intervals, respectively (Figure 6).

With respect to vision loss in the primary eyes cohort,

the Rheopheresis treatment group consistently had a smaller proportion of cases with ETDRS line losses at each postbaseline interval compared with the placebo-control group (Table V). At 12 months postbaseline, only 5.3% of Rheopheresis-treated eyes demonstrated a ≥3-line loss of BCVA compared to 28.6% of placebo controls (Figure 7). In the subgroup of Rheopheresis-treated primary eyes with baseline LogMAR acuity worse than 20/40, 57.9% improved to 20/40 or better at the 12-month postbaseline interval compared with only 14.3% of the

TABLE III: BASELINE LABORATORY VALUES BY TREATMENT GROUP

LABORATORY TEST	STUDY GROUP	N	MEAN	SD	MIN	MAX	*P* VALUE	NORMAL VALUES	
								LOW	HIGH
Albumin (g/dL)	Rheopheresis	28	4.16	0.25	3.8	4.9	.419	3.5	4.8
	Placebo	15	4.23	0.27	3.6	4.5			
$Alpha_2$-macroglobulin (mg/dL)	Rheopheresis	25	198.6	54.5	127	357	.843	131	293
	Placebo	13	202.4	55.5	124	315			
E-selectin (ng/mL)	Rheopheresis	25	40.6	14.7	17	66.4	.179	12.0	80.4
	Placebo	13	47.9	17.1	21.2	81			
Fibrinogen (mg/dL)	Rheopheresis	25	377.6†	139.2	87	776	.716	154	494
	Placebo	14	362.4†	92.6	267	551			
Hemoglobin (g/dL)	Rheopheresis	28	14.03	1.28	11.7	16.8	.807	11.5	17.0
	Placebo	15	14.13	1.32	12.3	16.7			
Hematocrit (%)	Rheopheresis	28	41.9	3.7	35.7	48.7	.488	34	50
	Placebo	15	42.7	3.5	36.6	48			
IgA (mg/dL)	Rheopheresis	28	282.6	106.4	113	532	.560	70	400
	Placebo	15	306.4	157.9	75	698			
IgG (mg/dL)	Rheopheresis	28	1048.2	238.7	576	1567	.995	700	1600
	Placebo	15	1047.7	245.2	697	1741			
IgM (mg/dL)	Rheopheresis	28	120.7	109.6	22	584	.429	40	230
	Placebo	15	120.3	62.5	51	300			
International normalized ratio	Rheopheresis	26	1.32*	1.13	0.9	6.8	.672	2.0	3.5
	Placebo	14	1.16*	0.43	0.9	2.6			
Platelets ($x10^3/\mu L$)	Rheopheresis	28	250.7	56.0	153	360	.375	140	415
	Placebo	14	267.1	55.4	173	354			
PT (sec)	Rheopheresis	25	16.4*	15.4	11.1	89.3	.464	9.0	12.7
	Placebo	14	13.9*	5.6	10.6	32.8			
aPTT (sec)	Rheopheresis	25	29.4	6.2	24	52	.416	23	39
	Placebo	14	27.4	3.0	24	35			
sICAM-1 (ng/mL)	Rheopheresis	25	299.5†	51.9	222.2	447	.805	114.7	306.4
	Placebo	13	295.2†	47.9	235.2	384			
Total cholesterol (mg/dL)	Rheopheresis	28	220.1*	37.3	155	292	.442	100	199
	Placebo	15	229.9*	43.7	150	354			
HDL-C (mg/dL)	Rheopheresis	28	54.2	14.7	30	85	.351	30	85
	Placebo	15	59.7	23.5	34	129			
VLDL-C (mg/dL)	Rheopheresis	26	37.0†	16.0	12	74	.361	5	40
	Placebo	14	32.4†	12.9	8	58			
LDL-C (mg/dL)	Rheopheresis	26	125.6†	34.4	73	192	.478	0	129
	Placebo	14	134.4*	42.3	65	244			
Von Willebrand factor activity (%)	Rheopheresis	24	115.3	47.6	51	226	.315	50	170
	Placebo	12	134.0	60.2	54	259			
Uric acid (mg/dL)	Rheopheresis	28	5.24	1.19	2.8	7.5	.011	2.4	8.2
	Placebo	15	4.26	1.05	1.9	5.8			
Total protein (g/dL)	Rheopheresis	28	7.23	0.42	6.4	8.5	.382	6.0	8.5
	Placebo	15	7.36	0.55	6.5	8.7			
Triglyceride (mg/dL)	Rheopheresis	28	205.5	104.4	61	492	.490	10	250
	Placebo	15	182.9	96.0	44	449			
Serum osmolality (mOsm/kg)	Rheopheresis	24	301.6*	8.7	285	318	.475	280	301
	Placebo	13	299.6†	6.0	288	309			
Viscosity serum (cP, relative to saline)	Rheopheresis	23	1.65	0.13	1.4	1.9	.108	1.6	1.9
	Placebo	12	1.78	0.31	1.5	2.7			
Viscosity whole blood (cP)	Rheopheresis	25	6.56*	1.33	4.5	10.8	.757	3.6	6.0
	Placebo	11		1.67	4.2	9.8			

*Exceeds limits.
†Highest quartile.

TABLE IV: COMPARISON OF MEAN CHANGE FROM BASELINE ETDRS BCVA RHEOPHERESIS TREATMENT VERSUS PLACEBO CONTROL

COHORT	N	MEAN LOGMAR LINE DIFFERENCE (AT 12 MO)	GROUP EFFECT F	GROUP EFFECT *P* VALUE*	TIME EFFECT F	TIME EFFECT *P* VALUE*
All eyes	85					
Primary eyes	43	1.6	12.22	.0011	1.41	.2560
All qualifying eyes	54	1.5	8.50	.0053	1.39	.2570
All eyes	85	1.7	9.49	.0028	0.97	.4093
All eyes with baseline BCVA worse than 20/40	56					
Primary eyes	28	3.0	12.70	.0014	1.31	.2928
All qualifying eyes	35	2.8	7.08	.0122	1.36	.2747
All eyes	56	3.2	8.55	.0050	1.10	.3565

**P* values calculated by ANOVA with repeated measures analysis (with unstructured covariance).

TABLE V: PRIMARY EYES: CHANGES IN BCVA OVER TIME

	3 MONTHS		6 MONTHS		9 MONTHS		12 MONTHS	
EFFICACY PARAMETER	TREATMENT	PLACEBO	TREATMENT	PLACEBO	TREATMENT	PLACEBO	TREATMENT	PLACEBO
N=	28	15	27	13	23	13	25	11
All treatment eyes								
Visual improvement								
≥+1 line	14 (50.0%)	3 (20.0%)	13 (48.1%)	3 (23.1%)	9 (39.1%)	6 (46.2%)	12 (48.0%)	3 (27.3%)
≥+1.5 lines	10 (35.7%)	1 (6.7%)	11 (40.7%)	3 (23.1%)	6 (26.1%)	2 (15.4%)	9 (36.0%)	2 (18.2%)
≥+2 lines	8 (28.6%)	1 (6.7%)	7 (25.9%)	2 (15.4%)	4 (17.4%)	0 (0.0%)	7 (28.0%)	2 (18.2%)
≥+2.5 lines	4 (14.3%)	0 (0.0%)	3 (11.1%)	0 (0.0%)	3 (13.0%)	0 (0.0%)	5 (20.0%)	1 (9.1%)
≥+3 lines	3 (10.7%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	3 (13.0%)	0 (0.0%)	3 (12.0%)	0 (0.0%)
Visual loss								
Loss of ≥3 lines BCVA	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)	1 (4.0%)	2 (18.2%)
Loss of ≥2 lines BCVA	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (7.7%)	1 (4.3%)	2 (15.4%)	2 (8.0%)	2 (18.2%)
Average line change								
From baseline*	1.16	0.19	1.15	-0.43	0.90	-0.20	0.74	-0.87
Difference between treatment groups†	0.97		1.58		1.10		1.61	
N=	19	9	19	7	16	8	19	7
BCVA <20/40 pretreatment								
Visual improvement								
≥+1 line	11 (57.9%)	1 (11.1%)	9 (47.4%)	1 (14.3%)	7 (43.8%)	2 (25.0%)	11 (57.9%)	2 (28.6%)
≥+1.5 lines	9 (47.4%)	1 (11.1%)	7 (36.8%)	1 (14.3%)	4 (25.0%)	0 (0.0%)	8 (42.1%)	1 (14.3%)
≥+2 lines	8 (42.1%)	1 (11.1%)	6 (31.6%)	1 (14.3%)	4 (25.0%)	0 (0.0%)	6 (31.6%)	1 (14.3%)
≥+2.5 lines	4 (21.1%)	0 (0.0%)	3 (15.8%)	0 (0.0%)	3 (18.8%)	0 (0.0%)	4 (21.1%)	0 (0.0%)
≥+3 lines	3 (15.8%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	3 (18.8%)	0 (0.0%)	3 (15.8%)	0 (0.0%)
Improvement to 20/40 or better	10 (52.6%)	1 (11.1%)	10 (52.6%)	1 (14.3%)	6 (37.5%)	1 (12.5%)	11 (57.9%)	1 (14.3%)
Visual loss								
Loss of ≥3 lines BCVA	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (12.5%)	1 (5.3%)	2 (28.6%)
Loss of ≥2 lines BCVA	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (14.3%)	1 (6.3%)	2 (25.0%)	1 (5.3%)	2 (28.6%)
Average line change								
From baseline*	1.35	-0.11	1.23	-1.49	1.11	-1.05	1.06	-1.91
Difference between treatment groups†	1.46		2.72		2.16		2.98	

*Positive number equals improvement; negative number equals loss.
†Positive number means treatment better than placebo.

placebo-control group (Figure 8). The proportions of cases demonstrating visual improvements or losses were similar in the all-qualifying-eyes (Table VI) and the all-eyes (Table VII) cohorts.

MORPHOMETRICS

Of the 43 primary eyes graded by the Fundus Photograph Reading Unit, a total of 10 primary eyes, 28.6% (8 of 28) of the Rheopheresis-treated cases, and 13.3% (2 of 15) of

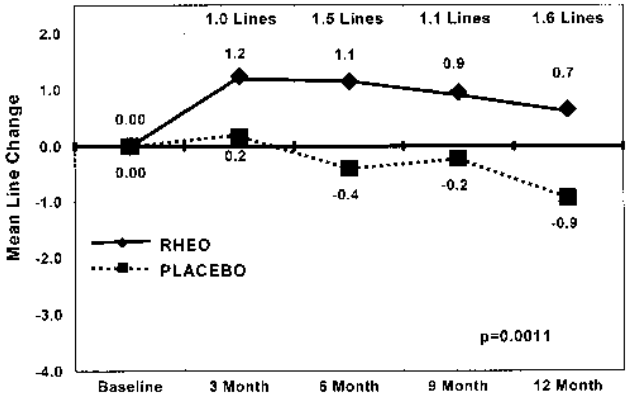

FIGURE 2
Mean ETDRS line change over time in the primary eyes randomized to receive Rheopheresis or placebo-control treatment.

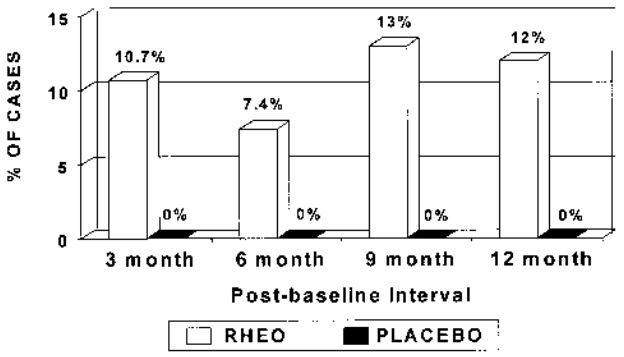

FIGURE 3
Proportion of cases with ≥3 lines of ETDRS BCVA improvement at each postbaseline interval in the primary eyes cohort of patients randomized to receive Rheopheresis or placebo-control treatment.

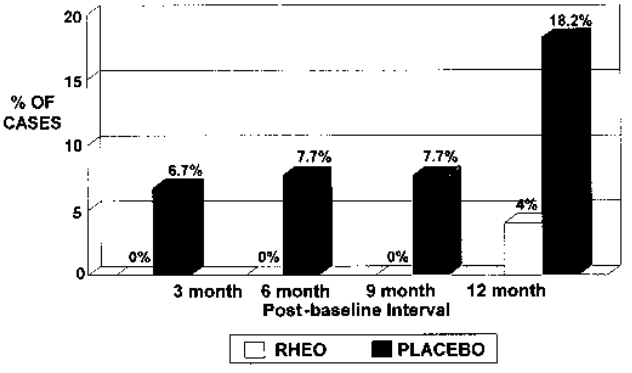

FIGURE 4
Proportion of cases with ≥3 lines of ETDRS BCVA loss at each post-baseline interval in the primary eyes cohort of patients randomized to receive Rheopheresis or placebo-control treatment.

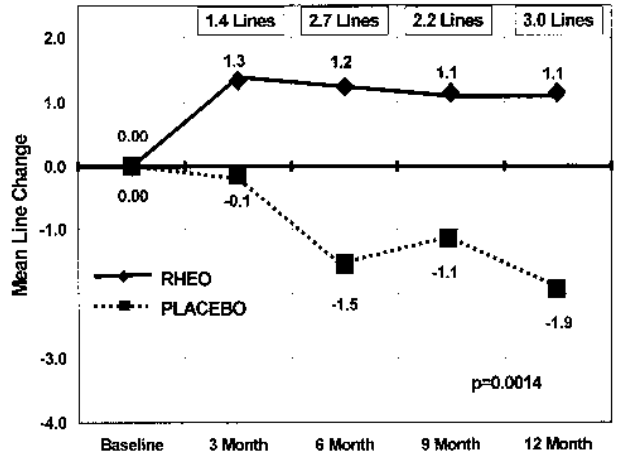

FIGURE 5
Mean ETDRS line change over time in subgroup of primary eyes with worse than 20/40 vision at baseline who were randomized to receive Rheopheresis or placebo-control treatment.

the placebo-control cases were found to have either a decrease in the number of drusen or drusen with a more atrophic (whiter) appearance over the course of the study (P = .28 with Fisher's exact test). In no case was a progression to nonexudative AMD documented.

SAFETY: REPORTING OF ADVERSE EVENTS

General

In the MIRA-1 interim analysis population, a total of 40 adverse events, both treatment-related (5) and non-treatment-related (35), were recorded during 343 treatments and over the 12-month postbaseline interval for the 43 patients subject to the analysis. Table VIII provides a listing of each reported event by treatment arm, Rheopheresis (RHEO=23) versus placebo control (PBO=17). Four ophthalmic events were documented, two in each study group. In the Rheopheresis treatment group, one treatment-related case of bilateral lid edema occurred and resolved spontaneously within 48 hours with application of warm and cold compresses. A mild non-treatment-related case of iritis was also reported, and it resolved without sequelae. In the placebo-control group, one case of unilateral lid edema was noted and one case of capsular opacity occurred. The most common problem encountered in the trial population involved the establishment and maintenance of adequate peripheral venous access in the Rheopheresis group (38 of 223 procedures [17%]). The use of A-V shunts, percutaneous intravascular catheters (ie, PIC lines), ports, or other means, while not medically contraindicated, was prohibited in the context of this FDA study.

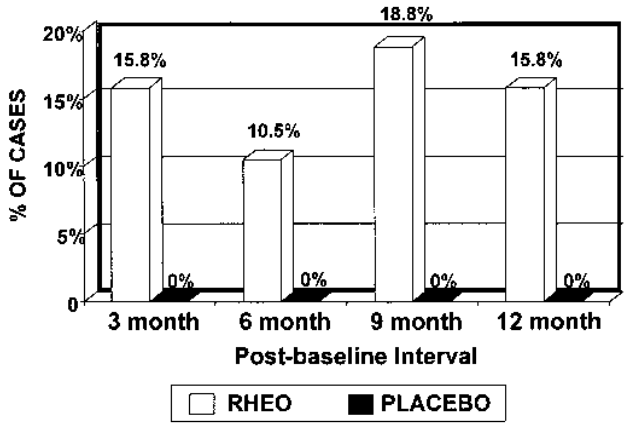

FIGURE 6
Proportion of cases with ≥3 lines of ETDRS BCVA improvement at each postbaseline interval in subgroup of primary eyes of patients with baseline BCVA of worse than 20/40 that were randomized to receive Rheopheresis or placebo-control treatment.

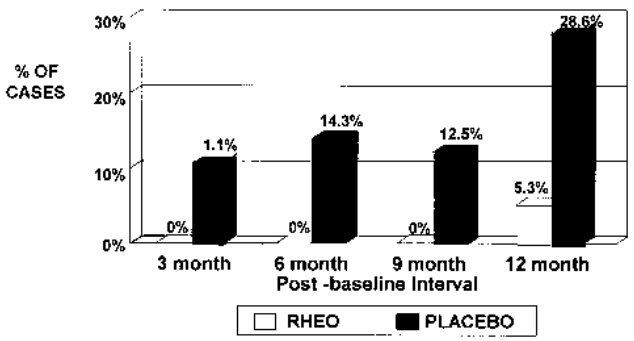

FIGURE 7
Proportion of cases with ≥3 lines of ETDRS BCVA loss at each postbaseline interval in subgroup of primary eyes of patients with baseline BCVA of worse than 20/40 that were randomized to receive Rheopheresis or placebo-control treatment.

Non-Treatment-Related Adverse Events

The incidence of reported non-treatment-related adverse events was significantly lower in the Rheopheresis treatment group (8.1%, 18 of 223) than the placebo-control group (17 of 120 [14.2%]) (P = .03). The incidence of serious non-treatment-related events for the Rheopheresis treatment group (5 of 223 [2.2%]) and the placebo-control group (2 of 120 [1.6%]) was similar (P = .30). Two distant deaths (one by suicide and one due to leukemia) were reported in the Rheopheresis treatment group. Both deaths occurred between the 9-month and 12-month postbaseline interval. No deaths occurred in the placebo-control group.

Treatment-Related Adverse Events

Treatment-related adverse events were observed in 2.2% (5 of 223) of Rheopheresis procedures and in 0% (0 of 120) of placebo-control treatments (P = .11). None of the five Rheopheresis-related events were serious, and none were unanticipated (Figure 9). All five nonserious Rheopheresis-related events were associated with either transient or self-limited changes in intratreatment blood pressure (hypotension, 2), fluid shifts (edema, 2), or vagal response (nausea, 1). No treatment-related hospitalizations or long-term treatment-related side effects or adverse events have been reported during this study.

DISCUSSION

THE MIRA-1 TRIAL

MIRA-1 is the largest double-masked apheresis trial ever undertaken. It is the first prospective trial to evaluate the

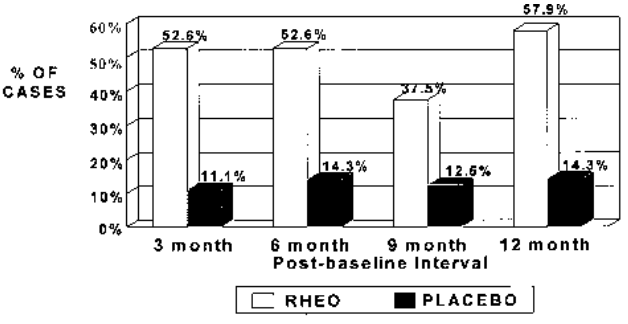

FIGURE 8
Proportion of cases with ETDRS improvements to 20/40 or better at each postbaseline interval in subgroup of primary eyes of patients with worse than 20/40 BCVA at baseline that were randomized to receive Rheopheresis or placebo-control treatment.

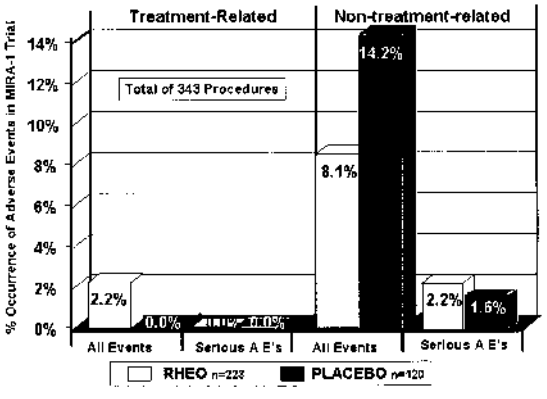

FIGURE 9
Occurrence of treatment-related and non-treatment-related adverse events in the 343 procedures performed in 43 patients randomized to receive Rheopheresis or placebo-control treatments reported as both serious and nonserious adverse events.

TABLE VI: ALL QUALIFYING EYES: CHANGES IN BCVA OVER TIME

EFFICACY PARAMETER	3 MONTHS TREATMENT	3 MONTHS PLACEBO	6 MONTHS TREATMENT	6 MONTHS PLACEBO	9 MONTHS TREATMENT	9 MONTHS PLACEBO	12 MONTHS TREATMENT	12 MONTHS PLACEBO
N=	36	18	35	16	30	16	32	13
All treatment eyes								
Visual improvement								
≥+1 line	18 (50.0%)	5 (27.8%)	16 (45.7%)	3 (18.8%)	13 (43.3%)	7 (43.8%)	16 (50.0%)	4 (30.8%)
≥+1.5 lines	13 (36.1%)	1 (5.6%)	14 (40.0%)	3 (18.8%)	9 (30.0%)	2 (12.5%)	12 (37.5%)	2 (15.4%)
≥+2 lines	9 (25.0%)	1 (5.6%)	10 (28.6%)	2 (12.5%)	7 (23.3%)	0 (0.0%)	10 (31.3%)	2 (15.4%)
≥+2.5 lines	4 (11.1%)	0 (0.0%)	3 (8.6%)	0 (0.0%)	4 (13.3%)	0 (0.0%)	5 (15.6%)	1 (7.7%)
≥+3 lines	3 (8.3%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	4 (13.3%)	0 (0.0%)	3 (9.4%)	0 (0.0%)
Visual loss								
Loss of ≥3 lines BCVA	0 (0.0%)	1 (5.6%)	1 (2.9%)	1 (6.3%)	1 (3.3%)	2 (12.5%)	1 (3.1%)	2 (15.4%)
Loss of ≥2 lines BCVA	1 (2.8%)	1 (5.6%)	1=(2.9%)	1 (6.3%)	2 (6.7%)	3 (18.8%)	2 (6.3%)	2 (15.4%)
Average line change								
From baseline*	1.02	0.31	0.93	-0.41	0.73	-0.36	0.82	-0.69
Difference between treatment groups†	0.71		1.34		1.09		1.51	
N=	24	11	24	9	20	10	23	8
BCVA <20/40 pretreatment								
Visual improvement								
≥+1 line	12 (50.0%)	2 (18.2%)	10 (41.7%)	1 (11.1%)	8 (40.0%)	2 (20.0%)	12 (52.2%)	2 (25.0%)
≥+1.5 lines	9 (37.5%)	1 (9.1%)	8 (33.3%)	1 (11.1%)	5 (25.0%)	0 (0.0%)	9 (39.1%)	1 (12.5%)
≥+2 lines	8 (33.3%)	1 (9.1%)	7 (29.2%)	1 (11.1%)	5 (25.0%)	0 (0.0%)	7 (30.4%)	1 (12.5%)
≥+2.5 lines	4 (16.7%)	0 (0.0%)	3 (12.5%)	0 (0.0%)	4 (20.0%)	0 (0.0%)	4 (17.4%)	0 (0.0%)
≥+3 lines	3 (12.5%)	0 (0.0%)	2 (8.3%)	0 (0.0%)	4 (20.0%)	0 (0.0%)	3 (13.0%)	0 (0.0%)
Improvement to 20/40 or better	11 (45.8%)	2 (18.2%)	10 (41.7%)	1 (11.1%)	7 (35.0%)	1 (10.0%)	13 (56.5%)	1 (12.5%)
Visual loss								
Loss of ≥3 lines BCVA	0 (0.0%)	1 (9.1%)	1 (4.2%)	1 (11.1%)	1 (5.0%)	2 (20.0%)	1 (4.3%)	2 (25.0%)
Loss of ≥2 lines BCVA	1 (4.2%)	1 (9.1%)	1 (4.2%)	1 (11.1%)	2 (10.0%)	3 (30.0%)	1 (4.3%)	2 (25.0%)
Average line change								
From baseline*	1.02	0.07	0.87	-1.31	0.64	-1.30	0.97	-1.78
Difference between treatment groups†	0.94		2.18		1.94		2.75	

*Positive number equals improvement; negative number equals loss.
†Positive number means treatment better than placebo.

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 preangiogenic AMD with soft drusen and elevated serum levels of selected hemorheologic factors. The results of the interim analysis of the first 43 intent-to-treat patients demonstrated a significant improvement in LogMAR BCVA through 12 months in the Rheopheresis-treated group relative to the placebo-control group (P = .001, repeated measures analysis).

POSTULATED MECHANISM(S) OF ACTION

Rheopheresis directly targets the elimination of known vascular risk factors and suspected pathophysiologically relevant factors of AMD by decreasing plasma viscosity and depleting the serum of soluble macromolecular species such as immune complexes, IgM, fibrinogen, LDL and VLDL cholesterol, von Willebrand factor, α_2-macroglobulin, and probably multimeric vitronectin, along with other acute phase reactants, chronic immunomodifiers, and cell signaling components.[17] These markers, however, should currently be regarded as epidemiologic risk factors. None have demonstrated any causal relationship with AMD. Indeed, our data remain insufficient to determine whether the presence or depletion of any of these compounds may prove to be predictive for determining an individual patient's potential susceptibility to obtain a therapeutic response from Rheopheresis.

Friedman and colleagues[18,19] have suggested a hemodynamic model of AMD pathogenesis in a series of papers. They hypothesize that impaired choroidal perfusion results from increases in vascular resistance in the choroid, possibly as a consequence of decreased compliance of the sclera and choroidal vessels with increased age combined with lipidization of Bruch's membrane and accompanying drusen biosynthesis. Such effects would

TABLE VII: ALL EYES: CHANGES IN BCVA OVER TIME

EFFICACY PARAMETER	3 MONTHS TREATMENT	3 MONTHS PLACEBO	6 MONTHS TREATMENT	6 MONTHS PLACEBO	9 MONTHS TREATMENT	9 MONTHS PLACEBO	12 MONTHS TREATMENT	12 MONTHS PLACEBO
N=	**56**	**29**	**54**	**25**	**46**	**25**	**50**	**21**
All treatment eyes								
Visual improvement								
≥+1 line	28 (50.0%)	7 (24.1%)	27 (50.0%)	5 (20.0%)	22 (47.8%)	10 (40.0%)	25 (50.0%)	6 (28.6%)
≥+1.5 lines	20 (35.7%)	2 (6.9%)	24 (44.4%)	4 (16.0%)	15 (32.6%)	3 (12.0%)	17 (34.0%)	3 (14.3%)
≥+2 lines	15 (26.8%)	2 (6.9%)	18 (33.3%)	3 (12.0%)	12 (26.1%)	1 (4.0%)	15 (30.0%)	3 (14.3%)
≥+2.5 lines	9 (16.1%)	1 (3.4%)	8 (14.8%)	0 (0.0%)	9 (19.6%)	1 (4.0%)	10 (20.0%)	2 (9.5%)
≥+3 lines	7 (12.5%)	1 (3.4%)	7 (13.0%)	0 (0.0%)	9 (19.6%)	1 (4.0%)	7 (14.0%)	0 (0.0%)
Visual loss								
Loss of ≥3 lines BCVA	0 (0.0%)	2 (6.9%)	1 (1.9%)	3 (12.0%)	1 (2.2%)	3 (12.0%)	1 (2.0%)	4 (19.0%)
Loss of ≥2 lines BCVA	3 (5.4%)	2 (6.9%)	2 (3.7%)	3 (12.0%)	2 (4.3%)	4 (16.0%)	3 (6.0%)	4 (19.0%)
Average line change								
From baseline*	1.12	0.21	1.16	-0.50	1.15	-0.03	1.02	-0.71
Difference between treatment groups†	0.91		1.66		1.18		1.74	
N=	38	18	38	14	32	15	36	12
BCVA <20/40 pretreatment								
Visual improvement								
≥+1 line	21 (55.3%)	3 (16.7%)	19 (50.0%)	2 (14.3%)	17 (53.1%)	3 (20.0%)	21 (58.3%)	3 (25.0%)
≥+1.5 lines	15 (39.5%)	2 (11.1%)	17 (44.7%)	2 (14.3%)	11 (34.4%)	1 (6.7%)	14 (38.9%)	2 (16.7%)
≥+2 lines	14 (36.8%)	2 (11.1%)	15 (39.5%)	2 (14.3%)	10 (31.3%)	1 (6.7%)	12 (33.3%)	2 (16.7%)
≥+2.5 lines	9 (23.7%)	1 (5.6%)	8 (21.1%)	0 (0.0%)	9 (28.1%)	1 (6.7%)	9 (25.0%)	1 (8.3%)
≥+3 lines	7 (18.4%)	1 (5.6%)	7 (18.4%)	0 (0.0%)	9 (28.1%)	1 (6.7%)	7 (19.4%)	0 (0.0%)
Improvement to 20/40	11 (28.9%)	2 (11.1%)	11 (28.9%)	1 (7.1%)	7 (21.9%)	1 (6.7%)	13 (36.1%)	1 (8.3%)
Visual loss								
Loss of ≥3 lines BCVA	0 (0.0%)	2 (11.1%)	1 (2.6%)	3 (21.4%)	1 (3.1%)	3 (20.0%)	1 (2.8%)	4 (33.3%)
Loss of ≥2 lines BCVA	3 (7.9%)	2 (11.1%)	2 (5.3%)	3 (21.4%)	2 (6.3%)	4 (26.7%)	2 (5.6%)	4 (33.3%)
Average line change								
From baseline*	1.25	0.10	1.27	-1.34	1.38	-0.71	1.32	-1.88
Difference between treatment groups†	1.15		2.62		2.08		3.21	

*Positive number equals improvement; negative number equals loss.
†Positive number means treatment better than placebo.

necessarily degrade the metabolic transport function of the pigment epithelium and other supporting posterior retinal tissues. Evidence for this hypothesis includes findings of increased scleral rigidity and increased pulsatility in the face of decreased end-diastolic blood flow velocities in the short posterior ciliary arteries in AMD patients. This hypothesis is further supported by the work of Grunwald and associates,[20] who, by using laser Doppler flowmetry, demonstrated a 33% decrease in choroidal blood velocity (P = .005) and a 37% decrease in choroidal blood flow (P = .0005) in patients with nonexudative AMD and at least 10 large soft drusen, when compared with an age-matched control group with no large drusen. Similarly, Ciulla and associates,[21] by using color Doppler imaging, demonstrated reduced ocular blood flow velocities in nonexudative AMD in the central retinal artery (P = .0007), suggesting the possibility of an extrachoroidal rheopathologic process. Similar decreases in choroidal blood flow with AMD have also been documented using fluorescein and indocyanine green angiography.[22-25]

These findings appear to suggest the possibility of a systemic influence in the development and progression of AMD. Recently, Mullins, Johnson, and others[26-28] suggested local immunobiosynthetic origins of drusen composed of compounds (complement, vitronectin, and others) also found in systemic circulation. Serum concentrations of such factors could potentially influence drusen composition as well. Putative notions of a possible connection between a molecular pathogenesis and AMD (drusen) and a systemic hemorheologic contribution become even more compelling when viewed in the context of our reported results.

Furthermore, inference of a possible systemic influence can be found in the reports of generalized risk factors that have been associated with AMD in several trials. These risk factors include smoking history,[29-36] systemic hypertension,[37] increased body mass index,[38,39] diets high in linoleic acid and certain lipids,[40,41] elevated fibrinogen lev-

TABLE VIII: MIRA-1 TOTAL REPORTED ADVERSE EVENTS*

EVENT†	RHEOPHERESIS	PLACEBO-CONTROL
Abdominal aortic aneurysm	1‡	
Abdominal pain	1‡	
Bigeminy	1‡	
Bronchospasm		1
Capsule opacity OD		1
Carpel tunnel syndrome	1	
Colon polyp		1
Common cold		1
Congestion, lung		1
Congestive heart failure		1‡
Decreased appetite	1	
Edema bilateral rms	1§	
Edema OU	1§	
Eyelid swelling		1
Fall on boat bruised groin area		1
Hand numbness	1	
Herpes zoster scalp	1	
Hip, leg, groin pain		1‡
Hyperglycemia		2
Hypertension	3	2
Hypotension	3 (2§)	
Hypovolemia	1	
Inguinal hernia		1
Leukemia, death	1‡	
Mild iritis	1	
Nausea	2 (1§)	
NSAID-induced gastritis	1	
Poison ivy		1
PVCs		1
Sinus infection	1	
Suicide, death	1‡	
Urinary tract infection		1
TOTAL ADVERSE EVENTS	23 of 223 (10.3%)	17 of 120 (14.2%)
TOTAL PATIENTS WITH ADVERSE EVENTS	16 of 28 (57%)	8 of 15 (53%)

NSAID, nonsteroidal anti-inflammatory drugs; PVC, premature ventricular contractions.
*Excludes venous access events (difficulty in establishing or maintaining adequate access); n = 38 in 13 patients.
†If the same event was reported more than once in the same patient, it was reported above only once.
‡Serious adverse event.
§Treatment-related.

els,[16,29] increased serum cholesterol,[13] increased hemorheologic factors,[16] elevated von Willebrand levels,[16] elevated α_2-macroglobulin levels,[17] and the presence of atherosclerosis itself.[15] Not all AMD studies, however, have consistently demonstrated an association with these cardiovascular and general health risk factors.[42, 43]

Brunner and colleagues[44] studied pulsatile ocular blood flow using a noninvasive quantitative assessment of the ciliary-choroidal blood flow developed by Langham and associates[45] immediately preceding and then subsequent to Rheopheresis treatments in 10 patients with AMD. They found a statistically significant 22% increase in ocular blood flow (P = .028). They attributed this finding to the other changes in hemorheologic parameters that they observed in that and other similar studies,[46] including (1) a 14% to 17% decrease in plasma viscosity, (2) a 12% to 18% decrease in whole-blood viscosity, and (3) a 52% to 66% decrease in erythrocyte aggregation. We agree that transient increases in blood flow may induce certain positive effects on microvascular perfusion. The durable improvements in BCVA documented in this and other studies, however, would seem to argue for a more complex mechanism than simply temporal increases in the supply of oxygen and nutrients provided by 10 to 21 weeks of therapy.

One possible answer is pointed out by Klingel and colleagues.[17] They state that the clinical consequences of impaired microcirculation are due to the complex interactive relationships between plasma components, blood cells, cells of the vessel wall (endothelium, vascular smooth-muscle cells, and fibroblasts), and the compartments of the surrounding tissues (cells and extracellular

TABLE IX: COMPARISON OF REPORTED SERIES OF RHEOPHERESIS MEMBRANE DIFFERENTIAL FILTRATION IN TREATMENT OF AMD

STUDY	CURRENT MIRA-1 STUDY		BRUNNER ET AL‡ ALL PATIENTS		BRUNNER ET AL‡ PATIENTS WITH SOFT DRUSEN	
TIME POSTBASELINE	12 MONTHS		12 MONTHS		12 MONTHS	
TREATMENT GROUP	TREATMENT	PLACEBO	TREATMENT	NO TREATMENT	TREATMENT	NO TREATMENT
N=	25	11	20	20	11	11
All treatment eyes						
Visual improvement						
≥+1 line	12 (48.0%)	3 (27.3%)	8 (40.0%)	1 (5.0%)	5 (45.5%)	1 (9.1%)
≥+1.5 lines	9 (36.0%)	2 (18.2%)	5 (25.0%)	1 (5.0%)	3 (27.3%)	1 (9.1%)
≥+2 lines	7 (28.0%)	2 (18.2%)	3 (15.0%)	1 (5.0%)	2 (18.2%)	1 (9.1%)
≥+2.5 lines	5 (20.0%)	1 (9.1%)	2 (10.0%)	1 (5.0%)	1 (9.1%)	1 (9.1%)
≥+3 lines	3 (12.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (9.1%)	1 (9.1%)
Visual loss						
Loss of ≥3 lines BCVA	1 (4.0%)	2 (18.2%)	2 (10.0%)	6 (30.0%)	0 (0.0%)	3 (27.3%)
Loss of ≥2 lines BCVA	2 (8.0%)	2 (18.2%)	3 (15.0%)	6 (30.0%)	0 (0.0%)	3 (27.3%)
Average line change						
From baseline*	0.74	-0.87	-0.21	-1.83	0.62	-1.33
Difference between treatment groups†	1.61		1.62		1.95	
N=	19	7	19	10	11	7
BCVA <20/40 pretreatment						
Visual improvement						
≥+1 line	11 (57.9%)	2 (28.6%)	8 (42.1%)	1 (10.0%)	5 (45.5%)	1 (14.3%)
≥+1.5 lines	8 (42.1%)	1 (14.3%)	5 (26.3%)	1 (10.0%)	3 (27.3%)	1 (14.3%)
≥+2 lines	6 (31.6%)	1 (14.3%)	3 (15.8%)	1 (10.0%)	2 (18.2%)	1 (14.3%)
≥+2.5 lines	4 (21.1%)	0 (0.0%)	2 (10.5%)	1 (10.0%)	1 (9.1%)	1 (14.3%)
≥+3 lines	3 (15.8%)	0 (0.0%)	1 (5.3%)	1 (10.0%)	1 (9.1%)	1 (14.3%)
Improvement to 20/40 or better	11 (57.9%)	1 (14.3%)	7 (36.8%)	1 (10.0%)	5 (45.5%)	1 (14.3%)
Visual loss						
Loss of ≥3 lines BCVA	1 (5.3%)	2 (28.6%)	3 (10.5%)	3 (30.0%)	0 (0.0%)	2 (28.6%)
Loss of ≥2 lines BCVA	1 (5.3%)	2 (28.6%)	3 (15.8%)	3 (30.0%)	0 (0.0%)	2 (28.6%)
Average line change						
From baseline*	1.06	-1.91	-0.22	-2.12	0.62	-1.26
Difference between treatment groups†	2.98		1.90		1.88	

*Positive number equals improvement - negative number equals loss.
†Positive number means Treatment better than placebo/no treatment.
‡Visual improvement and visual loss data were calculated from the raw pretreatment and posttreatment LogMAR scores reported in Table I.

matrix). In addition, physical factors such as continuous laminar flow and shear stress within the microvascular bed are variables that need to be considered. The investigators point out that when considering the potential molecular pathogenesis of AMD, it must be remembered that Rheopheresis decreases α_2-macroglobulin levels by 59%, IgM by 65% to 70%, fibrinogen by 43% to 47%, LDL by 57% to 66%, and total cholesterol by 46% to 53%, while only decreasing albumin by 4% to 6% and producing no significant change in hematocrit levels.[5,40] While single-treatment elimination induces changes in the serum levels of these macromolecules for at least 3 to 4 days, the Rheopheresis protocol (pulsed interval apheresis) is designed to induce a prolonged hemorheologic dysequilibrium that can result in a sustained clinical benefit for months[10] or even years.[12]

As with other forms of plasma apheresis therapies, Rheopheresis may perturb both hematologic and immunologic homeostasis. Rheopheresis induces a prolonged dysequilibrium that may affect both systemic and local cytokine production in the choriocapillaris and retinal pigment epithelium (RPE).[17]

Another proposal has suggested the possibility that serum levels of these high-molecular-weight compounds may correlate with excessive accumulations in either Bruch's membrane or the choriocapillaris in genetically susceptible individuals over time. Deposition of these high-molecular-weight compounds at the interface of Bruch's membrane and the RPE would likely interfere with the transport-diffusion characteristics across these membranes and may induce the release of angiogenic compounds from adjacent ischemic retinal tissues (RPE

TABLE X: OTHER EUROPEAN TRIALS OF RHEOPHERESIS FOR AMD

	INDICATION	SUBJECTS	TREATMENT	EFFICACY PARAMETERS	OUTCOMES
First open-label acute study	Patients with AMD (42% CNV)	31 Eyes 17 Patients	2 Rheopheresis treatments 2 days apart	Comparison of ETDRS visual acuity 1 day prior to first treatment and 1 day after second treatment	ETDRS acuity: 15/31 (48%) of eyes gained 1 or more lines of ETDRS acuity Mean change was 4.5 lines (P = .005)
Second open-label acute study	•Exudative AMD, not laser candidates •Nonexudative AMD	78 Eyes 42 Patients	2 Rheopheresis treatments 2 days apart	Comparison of ETDRS visual acuity 1 day prior to first treatment and 1 day after second treatment	ETDRS acuity: 42.3% of eyes gained ≥1 line and 21.8% gained ≥2 lines; only 1% lost 1 line of vision and none lost >1 line
Pilot randomized extended treated study	Patients with AMD: •Wet (not candidates for laser) •Dry	AMD: 18 eyes of 9 patients Controls: 15 eyes of 9 patients	10 Rheopheresis treatments over a period of 21 weeks	Comparison of ETDRS visual acuity 1 day prior to initial treatment and just before each of the subsequent treatments	ETDRS acuity: After initial treatment, mean improvement in ETDRS from baseline was 0.7 lines (vs 0.0 lines among controls). After final treatment, change in lines of ETDRS acuity was compared between treated and controls: median difference was 2.2 lines after final treatment

AMD, age-related macular degeneration; CNV, choroidal neovascular membrane.

and others). The Rheopheresis protocol provides a sustained decrease in the serum levels of many of these high-molecular-weight compounds. Such may induce an equilibrium shift of these materials out of Bruch's membrane and choriocapillaris tissues into the "plasma pool," thereby decreasing the rate of accumulation of these compounds. Potentially, this would improve the transport-diffusion characteristics of these macromolecules across these membranes, allowing improved oxygenation and nutrition of the overlying RPE and neurosensory retina, as well as promote removal of digested pigment wastes. This would putatively enhance neuroprotective injury repair activity as well as decrease the stimuli that promote gene-directed apoptosis (programmed cell death) and inhibit the local production of angiogenic factors leading to choroidal neovascular transformation (wet form of AMD).

Although both of these possible mechanisms of action are hypothetical, they are not without support. A recent study of 78 patients with AMD showed elevated levels of multiple rheologic factors.[16] This cross-sectional study compared consecutive AMD patients seen in a macula clinic with age-matched normal controls. Plasma viscosity, von Willebrand factor, and fibrinogen were significantly elevated in the AMD patients compared with the controls (P <.0001, P = .0004, and P <.0001, respectively). These hemorheologic elements are directly reduced or depleted by Rheopheresis treatment.

Unfortunately, our current understanding of Rheopheresis is insufficient to definitively answer questions regarding its mechanisms of action. The clinical results with Rheopheresis will be better understood with our increasing knowledge of pathogenic mechanisms of AMD. It is noteworthy, however, to recognize that this trial and completed studies and multiple case series have repeatedly demonstrated similar positive effects on vision and retinal function subsequent to intervention with Rheopheresis filtration.

PRECEDENT CLINICAL TRIALS

A number of German trials have reported on the efficacy of Rheopheresis in AMD.[8-12] Success in several uncontrolled case series led to the initiation of the first prospec-

TABLE XI: COMPARISON OF EFFICACY PARAMETERS IN UNIVERSITY OF UTAH PILOT STUDY GROUPS (2000 ANNUAL REPORT IDE# G970241)

RESULTS	ETDRS MEAN LINE CHANGE*	PEPPER SPEED SCORE CHANGE FROM BASELINE* MEAN(%)/MEDIAN(%)	VF-14 SCORE CHANGE FROM BASELINE* MEAN(%)/MEDIAN(%)	VISUAL SYMPTOM QUESTIONNAIRE (10 ITEMS) MEAN NO. OF ITEMS IMPROVED
Rheopheresis	1.8	31.5 / 34.2	7.23 / 12.5	3.3
"Sham"	1.2	0.33 / +19.8	-0.35 / 0.66	0.9
Control	0.5	6.76 / -13.6	-8.49 / -10.3	0.0
Rheopheresis vs control	*P* = .017	*P* = .04	*P* = .039	*P* < .01

*Positive value indicates improvement.

tive randomized controlled clinical trial in Germany (MAC-1). Brunner and colleagues[10] enrolled 40 AMD patients who were randomly assigned to receive 10 Rheopheresis treatments over a 21-week period or to the no-treatment control. The analysis of the 40 primary eyes demonstrated a mean difference in LogMAR BCVA of 1.57 lines between treatment and control groups immediately posttreatment (*P*<.01). The subset of all primary eyes with soft drusen (n = 22; 11 Rheopheresis, 11 control) demonstrated a mean difference of 2.33 lines between treatment and control groups posttreatment (*P*<.01). In 92.5% of these eyes, baseline ETDRS visual acuity was worse than 20/40. Therefore, it is not unexpected that the MAC-1 results should closely parallel those reported here. The visual results of the current study and the Brunner trial, both reporting at an average of 12 months postbaseline, are given in Table IX. In addition, MAC-1 investigated electrophysiologic parameters of the retina that showed significant improvement of photopic a wave of the electroretinogram (*P* = .009) and the flicker electroretinogram (*P* = .03) equivalent to functional improvement of the central photoreceptor complex. In a case series of 10 patients with high-risk AMD with soft drusen, improvement in visual acuity essentially identical to the MAC-1 trial was confirmed (Fell A, et al. *Investigative Ophthalmology and Visual Science* 2000;41:S181). Results from 11 patients reported after long-term follow-up with interval "booster treatments" demonstrated that the therapeutic effect of the initial treatment series can be maintained over more than 2 years.[12] Eyes suffering from "dry" AMD had a mean improvement in visual acuity of 2.5 EDTRS lines of BCVA after 24 months. This study suggested that after a mean period of 12 months follow-up, provision of two to four booster treatments could be considered, depending on an individual patient's clinical course.[12]

Table X summarizes the findings of three other European trials of Rheopheresis for AMD. The first and second open labeled trials demonstrated an acute effect on ETDRS acuity after only two Rheopheresis treatments 2 days apart. The randomized trial demonstrated a median difference in ETDRS line change between treatment and control group of 2.2 lines after 10 treatments were administered over a 21-week period. Improvement of the pulsatile ocular blood flow[44] and decrease of the arteriovenous passage time in patients with AMD after Rheopheresis treatments were demonstrated in separate trials.[9,11]

An FDA pilot Investigative Device Exemption (IDE) study of Rheopheresis was performed at the University of Utah (*Investigative Ophthalmology and Visual Science* 1999;40[4]:319). The inclusion criteria were similar to those of the current study, except that elevated baseline serum levels of hemorheologic factors were not considered. Thirty patients were randomized into three groups of 10 patients each: an active treatment group, a "sham" operation, and a no-treatment control group. The sham treatment consisted of circulating the patients' blood through PVC tubing, but not through the membrane differential filters. Continuously heparinized extracorporeal circuits, however, cause many macroproteins to aggregate and adhere to the plastic tubing. As such, the sham operation induced a partial treatment effect with a documented reduction of high-molecular-weight protein concentrations of approximately 10% to 12% of that occurring for the treatment group. Active treatment consisted of 10 Rheopheresis treatments over a 16-week period instead of eight treatments over 10 weeks, as in the current study. The results immediately following the treatment period are shown in Table XI. Significant differences between Rheopheresis and control groups were observed with regard to ETDRS acuity, Pepper speed-reading scores, and two visual function questionnaires.

Given the evidence for efficacy, no significant safety concerns, and the lack of alternative therapies, the Rheopheresis system has been approved for commercial use for AMD in the European Union and Asia. Postcertification studies are ongoing within the framework of an interdisciplinary quality management program, including the incorporation of an outcomes database registry, the RheoNet System.[47]

ORAL SUPPLEMENTS

Currently, several studies have demonstrated that laser photocoagulation, including that using photodynamic therapy with verteporfin, is useful in the treatment of some forms of angiogenic AMD.[48,49] For preangiogenic AMD, the only treatment that has been shown to have even limited efficacy is the use of zinc, high-dose vitamins C, A, and E, and beta-carotene.[4] The AREDS demonstrated that these oral agents decreased the development of advanced AMD and decreased severe vision loss from AMD by 25% in patients with baseline stage 3 or 4 nonexudative AMD. The patients enrolled in the MIRA-1 study would be considered to have fundus criteria that would qualify them as being in at least the grade 3 or 4 group according to the AREDS classification scheme.

It is important to note that patients in both the Rheopheresis treatment group and the placebo-control group of the current trial were provided with the same daily vitamin supplementation formula, and both groups were prohibited from using other vitamin supplements so that differential supplementation use would not be a confounding variable (See Table I, "Inclusion Criteria"). The MIRA-1 protocol provided for daily oral intake of the following: 400 mg of vitamin C (four times the recommended daily allowance [RDA]), 200 IU of vitamin E (six times the RDA), 40 mg of zinc (2.5 times the RDA), and 3,000 IU of beta carotene (1.8 times the RDA). Although these levels were considered suprathreshold at the time of the initiation of the trial, they represent only about half of those levels used in the AREDS study. Even so, the current data suggest that the observed positive effects of Rheopheresis on vision are, at minimum, additive to high-dose nutritional supplementation.

SAFETY

Patient tolerance to extracorporeal procedures, and to needlesticks in general, varies widely among individuals, depending on resting vagal tone and other predisposing factors. Establishing and maintaining competent antecubital venous access over a 2- to 4-hour extracorporeal procedure in elderly patients remains the most frequently encountered technical challenge of Rheopheresis for AMD (17% of cannulations in this analysis experienced difficulties with vascular access).

The principle of Rheopheresis is membrane differential filtration (MDF), which is a safe and established modality of therapeutic apheresis. MDF exhibits a side-effects profile similar to that of other forms of extracorporeal therapies. These effects are typically both transient and self-limited. Historically, the safety of MDF has been reported in a number of studies. Godehardt and associates[50] analyzed data from 1,702 ambulatory MDF-LDL-apheresis treatments of 52 patients at nine centers (Figure 10). No severe adverse events occurred. In 98% of MDF treatments, no adverse reactions occurred. Hypotensive episodes were observed in 2%. In a trial of Rheopheresis in 10 patients with ischemic stroke, no severe adverse events were reported in 120 procedures.[51] In the MAC-1 trial at the University of Cologne, 20 patients, with a mean age of 72.0 years, received a total of 200 Rheopheresis treatments. Hypotension was observed in 6%, and non-significant hemolysis occurred in 2.5% of treatments.[10] A current RheoNet-registry analysis performed in November 2001 analyzed 1,388 Rheopheresis treatments from 273 patients with the mean age of 70.1 years. This analysis documented technical problems occurring in 1.8% and adverse reactions in 1.5% of Rheopheresis treatments. The adverse reactions included mainly hypotensive episodes, a few allergic reactions, and several observations of hemolysis. No symptomatic hemolysis occurred (R. Klingel, unpublished data). In summary, no reports document the occurrence of any serious, long-term, or unanticipated treatment-related adverse events or side effects from the use of Rheopheresis.

This dearth of reported long-term adverse effects is expected owing to the rapid reequilibration of necessary plasma components that are transiently depleted during the Rheopheresis protocol.

Theoretical concerns of induced bleeding diatheses and immunocompromise are unlikely to be realized when adhering to a conservative protocol of eight pulsed, 100% plasma volume therapies delivered over 10 weeks. Such a protocol provides for adequate intervals of "therapeutic rest," as is commonly employed with other extracorporeal procedures developed over the past 30 years for other indications, and for which a significant body of relevant clinical experience has been obtained.[50,52,53]

OBSERVATIONS FOR FURTHER STUDY

Although the findings reported here have a high degree of statistical significance, our study group recognizes that a sample size larger than 43 patients is important to provide

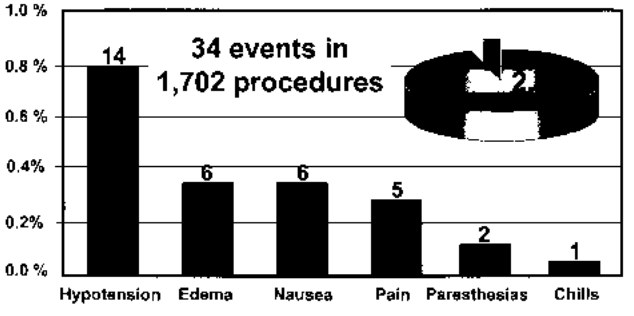

FIGURE 10

Membrane differential filtration (MDF) side effects reported in a multicenter series of 1,702 procedures. Typically, treatment effects are minor and self-limited.[50]

a basis for the widespread adoption of any novel technology such as Rheopheresis, whose specific mechanism of action is under investigation. Enrollment in MIRA-1 is thus continuing on to its planned 150-patient size. In addition, a sample size larger than 43 patients will be required to achieve significance in proportional differences in cases of eyes with greater than 2 or 3 lines of losses or gains in LogMAR BCVA. The final report will include all patients in the treated group as intent to treat.

Additional trials will be needed to further understand issues relating to Rheopheresis as a treatment for AMD, including (1) refining patient selection criteria, (2) determining retreatment efficacy, (3) determining mean duration of therapeutic effect and the periodicity of retreatment, (4) utility in secondary prevention of disease progression, (5) determining relevance of hemorheologic surrogate markers, and (6) the specific mechanism of action. The present study design did not provide information relative to determining the long-term efficacy beyond 1 year. Neither does it substantiate anecdotal accounts concerning the potential benefits of interval retreatment(s) on the maintenance of BCVA beyond 2 years. Also, MIRA-1 was not designed to study efficacy in cases with AREDS grades 1 and 2 AMD, and neither will it suffice as a secondary prevention trial for these earlier stages of the disease.

CONCLUSIONS

The results of this 12-month interval interim data analysis are encouraging, and several conclusions seem reasonable:

1. Rheopheresis as a treatment for selected patients with preangiogenic AMD appears to be safe and well tolerated by most patients.
2. Relative to placebo-control, Rheopheresis provided a statistically significant and clinically relevant improvement in ETDRS BCVA and provided a therapeutic effect that is evident immediately posttreatment; the benefit for treated eyes remains essentially stable throughout the 12-month period of the MIRA-1 trial.
3. Eyes diagnosed with BCVA worse than 20/40, characterized by ≥10 large soft drusen, and without evidence of neovascular change (in selected patients with high serum concentrations of certain soluble hemorheologic macromolecules) appear to be at increased risk for substantial vision loss over the ensuing 12-month period if left untreated.
4. The results of MIRA-1 closely approximate and support the findings of precedent trials.
5. A hypothesis based on our current knowledge of pathogenic mechanisms of the development and progression of AMD may be linked with the putative mechanism of action of Rheopheresis for AMD.
6. Continuation of the MIRA-1 trial is indicated.
7. Follow-up studies are suggested.

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ACKNOWLEDGMENTS

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Financial Disclosure Statement and Conflicts of Interest
Drs Brown, Davis, Deupree, Dewberry, Eaton, Martin, Mincey, and Sanders beneficially own stock or stock options in OccuLogix Corporation, the principal sponsor of the Study.

The total combined beneficial ownership of the principal retina investigators is less than 1% of the fully diluted shares outstanding. Drs Brown, Davis, Martin, and Sanders are significant investors; Dr Deupree has stock options as a member of the Scientific and Medical Advisory Board; Dr Davis is OccuLogix's Chairman, President, and Chief Executive Officer.

DISCUSSION

DR W. BANKS ANDERSON, JR. Diseases for which there is no effective established treatment have many remedies. Whether in herbal shops or in doctor's offices, such remedies are usually profit centers. How does one decide if such treatments do more than enrich their purveyors? One method is to observe a reproducible benefit of great magnitude as, for example, when penicillin was administered for pneumococcal pneumonia. Rheopheresis treatments for age-related macular degeneration in Cologne and Florida have not met this "great magnitude" test. To the credit of Dr Pulido and the other eight in the group, they are treating patients as part of a research protocol to assess the safety and efficacy of this therapy. The criteria for a study that scientifically establishes benefit are numerous, laborious, and expensive. Some of them are as follows: prospective, randomized and safe; entry criteria that allow extrapolation; masking of both the observers and the patients as to treatment; "n" large enough to establish significance; independent monitors for safety and data collection; independent masked image graders; no outcome-dependent financial effects on the participants and; methods and outcomes are reproducible by others.

This study is prospective, randomized, and seemingly safe. Except for one Asian, all in the study population are Caucasian. But since most AMD patients are Caucasian, the results would extrapolate to the affected population. Masking has been rigorous with study patients differing in that they have larger needle wounds. Recirculation of heparinized blood without the filters was not done as a control because it was felt that large molecule adherence to the plastic tubing, as seen in pilot studies, might contribute to a treatment effect. The results presented this morning are obtained from 43 subjects, 28 of whom are in the treatment group. The planned "n" is 150. The monitors and graders are independent. This is a multicenter trial and Dr Pulido's group does not have a major financial interest in a positive outcome; however, other groups in the study do have such an interest.

We have learned this morning that at one year, the treatment group differed from the controls by a statistically significant 1.6 lines of better vision. The 19 eyes with less than 20/40 at baseline averaged three lines of improvement. The study is ongoing.

Some questions I have for Dr Pulido are: Could heparin be responsible for the observed benefit? When do you predict completion of the 150-subject study? What is the cost of a course of treatment?

I congratulate the participating groups in electing to provide this new treatment for age-related dry macular degeneration in the context of a controlled and masked study.

DR JOHN T. FLYNN. What happened to the rheological criteria that allowed the patient to be entered into the study during the period of follow-up? Did the studies return to the baseline values or change significantly over time? The change would seem to play a role in what's happening.

DR PAUL R. LICHTER. I have a question in terms of your data and safety monitoring committee. You've shown a significance improvement in these first patients. What is the ethics of continuing to add patients to the study, since the untreated patients did considerably worse than the treated patients?

DR DONALD SANDERS (Dr Sanders was on the writing committee for this paper). I would like to address two of the issues. First, with regard to the data and safety monitoring committee: the FDA is the data and safety monitoring committee in device trials. Because of the controversy related to this technology in the ophthalmic community, it was felt that an "n" of 43 cases might not be sufficient. The study will be continued although the FDA has approved the treatment of the placebo patients after they complete the 12-month follow-up, in essence agreeing with Dr Lichter that the data is sufficiently compelling

that the placebo patients should be treated. Second, with regard to the rheological markers (total cholesterol, fibrinogen, and IgA): one of the possible ways that this technique works is to decrease plasma viscosity and therefore increase choroidal blood flow. With the procedure, the total cholesterol, IgA, and these large molecules transiently decrease, and the plasma viscosity has been demonstrated to decrease, probably for weeks. The subsequent increased choroidal blood flow possibly stops some sort of cascade causing the problem in AMD. Since we don't know what causes the etiology of AMD, however, we don't know why this is improving. The levels of those markers return to normal after the treatment is completed, although the effect appears to last a year.

DR JOSE S. PULIDO. I think Dr Lichter's question has been answered. As far as Dr Flynn's question about the rheological markers: Dr Sanders had alluded to the literature that indicates that these markers do transiently decrease a tremendous amount following rheopheresis but subsequently, with time, rise. We don't have specific data yet for the patients in this study, but it is probably the same as occurs in other patients that have been treated with rheopheresis. I appreciated Dr Banks Anderson's comments. Heparin was used in the patients that were undergoing treatment and was not used in the patients that were in the placebo group. The amount of heparin used is 5,000 units, which is the amount that you need for initial heparinization. The subsequent amount that's needed while you're on the treatment, however, is a low amount. With a half-life of about 30 minutes for heparin, there is enough heparin to act in a therapeutic fashion for about 5 hours following treatment. I don't think the amount and time the treated patient was on heparin are substantial, but I cannot discount the fact that heparin might have some action exclusive of the study. On the other hand, one could then also argue that just having the patient's blood circulate through a machine, exclusive of a filter, might be the reason there was efficacy as well.

The results of this study may be completed by next year; the company would like to see it even faster. As far as cost is concerned: I don't know what the cost is, and, as an academic physician, I am not concerned about the cost right now. My concern is to make sure that this study is completed ethically and expeditiously. Just as in the issue of photodynamic therapy, the quality-adjusted life per year cost is a potentially significant factor. Dr Sanjay Sharma showed that for photodynamic therapy, if one eye is affected with choroidal neovascularization and the other eye is not, the cost is about $100,000 per quality-adjusted life-years. This is very cost-ineffective compared with other medical therapies. If the study continues to show efficacy and if the FDA does approve this for the treatment, we hope that the company will keep the cost within reasonable range to make the quality-adjusted life-year cost reasonable.