

COMPLEMENTARY THERAPY ASSESSMENT APHERESIS FOR AGE-RELATED MACULAR DEGENERATION

May 2003

SUMMARY

INTRODUCTION TO THE TOPIC

Apheresis with membrane differential filtration for age-related macular degeneration (AMD) is a form of plasmapheresis currently under investigation in a prospective, randomized treatment trial designed, sponsored, and directed by Vascular Sciences Corporation (Tampa, Florida). This study is designed to enroll 180 specifically selected patients in one of 12 centers. Apheresis with membrane differential filtration for AMD is only available in the United States through enrollment in this clinical trial. Complete enrollment criteria are listed at <http://www.vascularsciences.net>.

CONCLUSIONS

Apheresis with membrane differential filtration for AMD is currently undergoing a double-masked, randomized clinical trial based on the results of two small randomized clinical trials, case reports, and unpublished anecdotal evidence. Once completed, this clinical trial may help determine if patients with non-neovascular AMD in this select group are stabilized or improved by this therapy. Physicians should exercise caution in recommending this therapy until final results from this study are available.

POTENTIAL BENEFITS

If the current trial is successful, there is potential for this therapy to preserve or improve vision in a subset of patients with non-neovascular AMD who meet specific criteria.

POTENTIAL RISKS

Available data suggest a 2 to 4 percent treatment-related complication rate during therapeutic apheresis. Complications include paresthesias, hypotension, nausea, and dizziness, all of which have been minor and transient. No serious long-term complications or side effects have been reported. Economic risk is not assessed in this report because the charges for the treatment, if approved, are not known.

REPORT

DESCRIPTION OF THE TECHNOLOGY

Therapeutic apheresis has been used for 30 years in the treatment of some systemic disorders such as Guillain-Barre syndrome and myasthenia gravis.^{1,2} The method of apheresis for patients with AMD discussed in this assessment consists of sequential apheresis using membrane differential filtration (MDF). In this technique, venous blood is pumped through a filter that separates the plasma from the cells. The plasma is then passed through a second filter that selectively removes high molecular-weight proteins. The remaining plasma is remixed with the cells and returned to the patient through a second peripheral venous access.

PRESUMED MECHANISM OF ACTION

Currently, there is no established link between either blood viscosity or the concentration of macromolecules and AMD. However, in systemic vascular beds, there is a suggestion that macromolecules may cause endothelial cell dysfunction.³ There are some data that suggest the hypothesis that a similar pathogenic process in the choriocapillaris may contribute to AMD.⁴ Two papers discuss the role of vitronectin, an adhesive glycoprotein, in the formation of human ocular drusen, and they advance the theory that vitronectin plays a role in the pathogenesis of AMD.^{5,6}

Perfusion of tissue beds depends on capillary blood flow and endothelial cell function. The main determinants of blood flow through a vessel are vessel diameter, pressure gradient, plasma viscosity, red blood cell (RBC) aggregation, and plasma concentration of certain blood constituents. Altering the vessel diameter or pressure gradient may not be possible within the choriocapillaris; however, decreasing plasma viscosity and RBC aggregation might increase flow through the choriocapillaris and improve perfusion of the macula. The possible improvement in choriocapillary blood flow and capillary endothelial cell function might enhance delivery of glucose, oxygen, and other nutrients to macular and retinal cells and facilitate removal of waste products. This possible increased blood flow and improved perfusion may enhance functions of the retinal pigment epithelium and photoreceptor cells. It is unknown if there are adverse effects from increasing the blood flow.

DEFINITION OF THE PROBLEM

Age-related macular degeneration is a disorder of the macula that occurs most often in patients 50 years old or older, and is the leading cause of irreversible central visual loss in Caucasians in this age group in the United States. Using the 1990 U.S. Census, approximately 750,000 people over 65 years of age were estimated to have severe visual impairment in one or both eyes from AMD,⁷ the majority of whom have the non-neovascular (atrophic) form. There is no established treatment for non-neovascular AMD. The etiology of AMD is unknown, but there may be diverse pathogenic processes, including a genetic component.⁸

FDA STATUS/LEGAL STATUS

Apheresis with membrane differential filtration for AMD is only available in the United States by enrolling in a prospective, double-masked, randomized clinical trial designed, funded, sponsored, and directed by Vascular Sciences Corporation (Tampa, Florida). The filtration device is being tested under an Investigational Device Exemption (IDE) from the FDA. Enrollment criteria include:

- Best spectacle-corrected visual acuity between 20/32 and 20/125 (ETDRS chart).
- Age 50 to 85 years with non-neovascular AMD with specifically defined large soft drusen.
- Elevated baseline serum concentrations of two of the following three factors: a total serum cholesterol level of greater than or equal to 200 mg/dl, a total serum fibrinogen level of greater than or equal to 300 mg/dl, or a total serum immunoglobulin A (IgA) level greater than or equal to 200 mg/dl.

Complete enrollment criteria are listed at www.vascularsciences.net/index2.html.

Enrollment of 180 patients in one of 12 centers is underway; two centers have completed their enrollment. Follow-up for one year is mandated in the trial protocol. Preliminary results have been presented.⁹

SUMMARY OF EVIDENCE

Search Methods

A MEDLINE search from 1966 to 1999 was conducted using the key terms plasmapheresis, artificial membranes, rheology, and macular degeneration. An EMBASE search from 1974 to 1999 was conducted using the same terms. An update search in MEDLINE and EMBASE from 1999 to 2002 was conducted in February 2003 using the same search terms.

Treatment Rationale

There is some support for the hypothesis underlying the treatment rationale in studies that have been summarized in a recent review article.⁸ However, an observational study not included in the review article does not support this hypothesis.¹⁰ In this study, the authors failed to find any link between atherosclerosis and its risk factors and prevalence of retinal lesions to explain the differing frequencies of age-related maculopathy between African Americans and Caucasian Americans.¹⁰ In addition, findings from a case-control study suggest that neovascular AMD is associated with moderate to severe hypertension, but non-neovascular AMD was unrelated to hypertension or cholesterol level.¹¹

Statistical Issues and Study Design

Results have been reported for three randomized controlled trials.^{12, 13, 9} Earlier investigations reported uncontrolled series of patients with maculopathies of different origins.^{14, 15} Other reports on this therapy are anecdotal and/or reported in abstract form only.

Specification of Level of Evidence

Two of the randomized controlled trials^{12, 13} are graded as Type II evidence because of uncertainty about the adequacy of the sample size and control group. Type II evidence generally consists of randomized, controlled trials with design flaws, well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, preferably from more than one center, and multiple-time series with or without the intervention. The third randomized controlled trial report⁹ was presented at the 2002 annual meeting of the American Ophthalmological Society and consists of an interim analysis of results from 43 patients; the planned total enrollment in the trial is 180 patients. As

this report represents preliminary information from the trial and was not subject to the peer review process, it is rated as Level III evidence. Level III evidence includes descriptive series, case reports, and reports of committees or organizations.

REPORTED BENEFITS

A preliminary report of the randomized controlled multicenter trial in the United States gave results of treatment in 43 patients, 28 receiving apheresis and 15 placebo-controlled patients.⁹ These results were presented at a meeting and were not subject to the peer review process (Level III evidence). Enrollment criteria are listed above. Patients received 8 apheresis or placebo procedures over 10 weeks. At one year, the mean LogMAR line difference between the treatment group and the control group was 1.6 lines ($P=0.001$); 1 treatment eye had a ≥ 3 -line loss of BCVA compared to 2 eyes in the control group. In a subgroup of eyes with baseline LogMAR worse than 20/40, 13 of 23 improved to 20/40 or better at one year compared to 1 of 8 in the placebo group. The changes in visual function were compared to baseline pre-treatment levels of visual acuity measured by ETDRS (LogMAR) chart and a standardized refraction and visual acuity protocol. All patients enrolled in the trial received the same daily vitamin oral supplement.

There is one study in the German literature in which 10 patients (18 eyes) received apheresis with membrane differential filtration and 10 patients (18 eyes) served as a control group.¹² Patients enrolled had either non-neovascular or neovascular AMD. In each group 8 out of 18 eyes showed subfoveal subretinal neovascularizations. The main outcome measure was best corrected ETDRS visual acuity measured by forced choice method. The treatment group received 10 treatments over 21 weeks. This group had a mean improvement of 1.1 (SD 1.9) lines immediately after treatment and the control group had a loss of 0.6 (SD 1.7) lines over the same period ($P < 0.01$). The two groups had a difference of 0.5 lines in long term follow-up (8-30 months) without retreatment, which was not statistically significant.

A study from the same investigators reported on 40 patients, 20 receiving apheresis with membrane differential filtration, and 20 patients serving as a control group receiving no treatment.¹³ It is not stated if this group includes patients from the earlier report. Patients enrolled had either non-neovascular or neovascular AMD. In each group, 9 patients showed subretinal neovascularization. The main outcome measure was best corrected ETDRS visual acuity using line assessment and the forced choice method. The treatment group received 10 apheresis procedures over 21 weeks. Final visual acuity measured at 24 hours following the last treatment showed a nonsignificant improvement of 0.63 lines (SD 1.8, $P=0.14$) on ETDRS charts while the control group had a loss of 0.94 lines (SD 1.7, $P=0.02$). The changes in visual function were measured in comparison with the baseline pre-treatment levels of visual acuity.

REPORTED RISKS

Available data suggest a 4 percent immediate adverse event rate during therapeutic apheresis for nonophthalmologic indications.^{2, 16, 17} Adverse effects reported have been minor and transient, and they include paresthesias, hypotension, nausea, and dizziness. No serious longstanding complications or side effects have been reported.

In the case series reported by Brunner of 36 patients who received apheresis for maculopathy, five patients (14%) had symptoms of hypocalcemia because of the anticoagulant, and three (8%) had hypotensive episodes (recorded blood pressure reading of less than 90/60 mmHg).¹⁵ In the report

from the United States trial, treatment-related adverse events were observed in 2.2% (5/223) of apheresis procedures and in none of the placebo-control procedures.⁹ No serious or longstanding treatment-related adverse events were reported.

Appropriate training for plasmapheresis procedures is necessary.

Economic risk is not assessed in this report because the charges for the treatment, if approved, are not known.

QUESTIONS FOR SCIENTIFIC INQUIRY

Several questions about apheresis for AMD need to be addressed.

- The basic hypothesis for the treatment is that improvement in microvascular blood flow and perfusion will improve visual function in patients with AMD. There is no consensus on the reproducibility of current methods to measure ocular blood flow. Do microvascular blood flow, perfusion, or other abnormalities play a role in the pathogenesis of AMD?
- If the current study demonstrates efficacy, at what stage of non-neovascular AMD pathogenesis will this treatment be most appropriate? Will it be effective for other forms of AMD?
- Are there long-term side effects of altering the concentration of blood constituents using this therapy?
- How long are benefits maintained? Are repeat treatments necessary? What is the ideal number and frequency of treatments to obtain or maintain any gains in visual acuity?
- How would this treatment compare with other therapies currently available or under investigation?

CONCLUSIONS

Apheresis with membrane differential filtration for AMD is currently undergoing a double-masked, randomized clinical trial based on the results of two small randomized studies, case reports, and unpublished, anecdotal evidence. Once complete, this clinical trial may help determine if patients with non-neovascular AMD in this select group are stabilized or improved by this therapy. Physicians should exercise caution in recommending this therapy until final results from this study are available.

DEVELOPMENT OF COMPLEMENTARY THERAPY ASSESSMENTS

Complementary, or alternative therapies, are a growing part of health care in America. Americans spend an estimated \$14 billion a year on alternative treatments. Most U.S. medical schools offer courses in alternative therapies. The editors of the *Journal of the American Medical Association* announced that publishing research on alternative therapies will be one of its priorities. More scrutiny and scientific objectivity is being applied to determine whether evidence supporting the effectiveness of complementary and alternative therapies exists.

The National Institutes of Health National Center for Complementary and Alternative Medicine has broadly defined complementary and alternative medicine as those treatments and health care practices that are not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies. The Cochrane Collaboration Complementary Medicine Field defines complementary medicine as including all such practices and ideas which are

outside the domain of conventional medicine in several countries and defined by its users as preventing or treating illness, or promoting health and well being. These practices complement mainstream medicine by 1) contributing to a common whole; 2) satisfying a demand not met by conventional practices; and 3) diversifying the conceptual framework of medicine.¹⁸

In the fall of 1998, the Board of Trustees appointed a Task Force on Complementary Therapy to evaluate the peer-reviewed scientific literature on complementary therapies in eye care and develop an assessment on their safety and effectiveness in order to inform ophthalmologists and their patients. A scientifically grounded analysis of the data will help ophthalmologists and patients evaluate the research and thus make more rational decisions on appropriate treatment choices.

The Academy believes that complementary therapies should be evaluated similarly to traditional medicine: evidence of safety, efficacy, and effectiveness should be demonstrated.¹⁹ Many therapies used in conventional medical practice also have not been as rigorously tested as they should be. Given the large numbers of patients affected and the health care expenditures involved, it is important that data and scientific information be used to base all treatment recommendations. In this way, we can encourage high-quality, rigorous research on complementary therapies.²⁰

Ideally, a study of efficacy compares a treatment to a placebo or another treatment, using a double-masked controlled trial and well-defined protocol. Reports should describe enrollment procedures, eligibility criteria, clinical characteristics of the patients, methods for diagnosis, randomization method, definition of treatment, control conditions, and length of treatment. They should also use standardized outcomes and appropriate statistical analyses.

The goal of these assessments is to provide objective information about complementary therapies and to provide a scientific basis for physicians to advise their patients, when asked.

To accomplish these goals, the assessments, in general, are intended to do the following:

- Describe the scientific rationale or mechanism for action for the complementary therapy.
- Describe the methods and basis for collecting evidence.
- Describe the relevant evidence.
- Summarize the benefits and risks of the complementary therapy.
- Pose questions for future research inquiry.
- Summarize the evidence on safety and effectiveness.

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ADDITIONAL RESOURCES

The following sites have additional information, including new treatments for AMD under evaluation in clinical trials.

National Eye Institute

<http://www.nei.nih.gov/neitrials/index.htm>

American Society of Retina Specialists

<http://www.vitreoussociety.org/>

The Retina Society
The Macula Society
Macular Degeneration Foundation

<http://www.retinasociety.org/>
<http://www.maculasociety.org>
<http://www.eyesight.org/index.html>

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Approved by the Quality of Care Secretariat January 30, 2000
Revision December 2001
Approved by the Quality of Care Secretariat December 25, 2001
Revision March 2003
Approved by the Quality of Care Secretary May 2, 2003

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