



# ET Close-up

## Rheopheresis – Ready for prime time? By Nick Lane PhD

Is there a rational basis for using rheopheresis to treat age-related macular degeneration? Will it really work? And if it does work, when might patients hope to benefit? *EuroTimes* investigated the current controversy surrounding this experimental therapy.

**D**r W Banks Anderson, Jr., put it well: “Diseases for which there is no effective established treatment have many remedies. Whether sold in herbal shops or in doctor’s offices, such remedies usually make a profit. How does one decide if such treatments do more than enrich their purveyors?”

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Dr Anderson was building up to comment on the use of rheopheresis to treat dry AMD – a condition that has no effective treatment beyond the AREDS formula of antioxidant supplements plus zinc, and a treatment with a troubled history.

Rheopheresis was developed by researchers at the University of Cologne in Germany in the early 1990s. There was always a whiff of voodoo about it – blood is removed and filtered in a technique similar to renal dialysis,

then re-infused back into the patient. Even if it did work, only a few ophthalmologists were prepared to hazard a guess as to why. Indeed, at the time, only a few were convinced that AMD is at least in part a systemic syndrome with parallels to other microcirculatory deficits such as diabetic foot disease.

The doubts were compounded by the negative publicity surrounding a 1998 medical investigation into the professional conduct of Richard Davis Jr, MD, the founder of Rheotherapy Centres of Largo, Florida, and later chairman, president and CEO of OccuLogix Corporation. Elias Vamvakas, former CEO of TLC Vision Corporation, recently replaced him as CEO and President at OccuLogix.

Dr Davis had visited Professor Richard Brunner MD, at the University of Cologne and had been impressed by his clinical results. Returning to America, Dr Davis now claimed that rheotherapy was a ‘revolutionary’ treatment for AMD, and “had been shown to be effective in the vast majority of patients with macular degeneration who had undergone the treatment.”

The Florida Board of Medicine begged to differ, stating that Davis’s claims were unsubstantiated; that the procedure was ‘experimental’; and that the practice constituted “an immediate and serious danger to the health, safety and welfare of the public.” Some eminent retinal specialists were just as scathing. Philip Rosenfeld, MD, at the University of Miami, said at the time “These guys are charging people \$20,000 for a treatment that doesn’t work.”

In the event, Dr Davis was permitted to continue treating AMD patients, but only in the context of an FDA-approved clinical trial.

Since 1998, two small, randomised controlled clinical trials have been completed, while a third, the FDA-approved MIRA-1 trial (Multicenter Investigation of Rheopheresis for AMD), is still ongoing. The number of patients whose data have been analysed from these trials so far is about

120, too small for any conclusive verdict on efficacy; but the results are consistent in themselves and do suggest efficacy.

As one of the investigators, David Boyer, MD, of the Retina Vitreous Associates, Beverly Hills, California, told *EuroTimes*, “In the early days, some people were making claims that were unsubstantiated, and that alienated some folks. But now that we’re carrying out a properly designed clinical trial, people are more open-minded about the outcome. I think there is a rational basis for this treatment, and of course I do want it to work, but I wouldn’t want to make any claims until we have the final analysis.”

### How does rheopheresis work?

A few years ago, many interested clinicians were willing to admit that they had “no idea” exactly how rheopheresis worked. This honest puzzlement only added to the stigma surrounding the treatment. But since the late 1990s, some careful experimental studies have helped to clarify the mechanism of action of rheopheresis. There’s no longer any need to talk of voodoo, although there are still a few big unknowns.

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Reinhard Klingel MD, PhD., a nephrologist at the Aphaeresis Research Institute in Cologne, told *EuroTimes*. “But in the meantime we have a lot of good information. The key lies in the interactions between the RPE, Bruch’s membrane and the choroidal vessels. Rheopheresis alters the dynamic equilibrium in these vessels, and there are signs that it can reduce oedema, and even reverse drusen formation to some extent. That’s why we sometimes see visual improvements.”

The procedure filters the entire blood supply of the patient, over a period of about two to four hours, depending on the patient’s size and quality of venous access. Treatments consist of establishing two IV lines, one in each forearm. The patient’s blood is routed through an aphaeresis device containing two filters, one to separate plasma from whole blood, and the other to sieve high molecular-weight lipids and proteins. After filtration, the reconstituted whole blood is pumped back into the patient’s other arm through a sterile closed circuit.

“As a nephrologist I can imagine this technique might look frightening to ophthalmologists,” Dr Klingel commented to *EuroTimes*. “It’s the same the other way around – some ophthalmic surgery terrifies me. But rheopheresis is basically a similar technique to dialysis, so nephrologists have had a great deal of experience. Unlike dialysis patients, people with dry AMD are generally pretty healthy – they don’t have as many other comorbidities. We’ve found rheopheresis to be safe and well-tolerated in AMD patients.”

Dr David Boyer has also found rheopheresis to be “an acceptably safe modality of treatment.” In the on-going FDA-approved trial of which he is an investigator, only a small proportion of patients have had any adverse events, with no significant differences between the two groups.

“In these elderly patients, establishing and maintaining venous access over a two to four hour extra-corporeal procedure remains the most difficult

challenge,” he said.

But why filter blood? The main rheofilter targets a bandwidth of high molecular-weight complexes (over about 500 kDa) including immune complexes such as IgM, LDL-cholesterol, a2-macroglobulin, fibrinogen and von Willenbrandt Factor. Smaller plasma proteins like albumin and HDL-cholesterol are relatively unaffected. For example, most large complexes are depleted by about 40% to 60%, while albumin levels fall by only a few per cent.

Many of the high molecular weight complexes depleted by rheotherapy are associated with immune and haemorheological processes, which in turn affect the interactions between the endothelium and circulating blood. Depleting large complexes lowers blood viscosity, improving blood flow and tissue oxygenation.

According to Dr Klingel, the better oxygenation probably assists the phagocytic action of the RPE cells, which engulf debris from the sensory retina and pass on the waste products via the choroidal circulation. “Phagocytosis is extremely dependent on oxygen levels, so we think that rheopheresis probably aids waste disposal, and this affects drusen formation.”

Doppler flowmetry has shown that choroidal blood flow falls by more than a third in AMD patients; and rheopheresis lowers full blood viscosity by 12% to 18% and erythrocyte aggregation by 50% to 60%. The remaining mystery relates to the long-term effect of rheopheresis: a series of pulsed treatments over a 10 or 20-week period leads to benefits that seem to persist for a full year, if not longer.

“Plasma levels of all the high molecular-weight complexes filtered return to normal within a few days of treatment, and yet the benefits persist much longer”, Dr Klingel told *EuroTimes*. “At the moment we don’t know why.”

Dr Boyer concurred. “I can only think that we’re affecting a dynamic equilibrium somehow. Perhaps we’re changing the circulation, or altering apoptosis in some way; I don’t know. Rheopheresis does seem to have

lasting benefits, but before we can establish exactly why, we need to prove the clinical effect.”

## The evidence base

The first two small randomised, controlled clinical trials were completed soon after the Florida Board of Medicine investigation, and despite the uncertainties inherent to their small size, seemed to bear out some degree of positive efficacy. The first of these trials, MAC-I, was carried out by Dr Richard Brunner and colleagues at the University of Cologne. They enrolled 40 patients with AMD into two groups—treatment and no-treatment control. More than 90% of the patients had an ETDRS best-corrected visual acuity (BCVA) at baseline of worse than 20/40. The primary endpoint was BCVA. The results were published in *Retina* 2000; 20 (5): 483-91.

Rheopheresis patients were treated ten times over a period of 21 weeks. The control group showed a mean deterioration of 0.94 lines, while the treatment group showed an improvement of 0.63 lines, a mean difference of 1.57 lines immediately post-treatment ( $p < 0.01$ ). This benefit was sustained over a full year, with a difference in BCVA of 1.62 lines at 12 months. In the subgroup of patients with soft drusen (11 in each group), the difference between the groups was slightly greater, 2.33 lines post-treatment, falling to 1.95 lines at 12 months.

Similar results were obtained by Mano Swartz, MD., and colleagues in their FDA pilot study at the University of Utah, presented at ARVO in 1999 and published in *Investigative Ophthalmology and Visual Science* 1999; 40: (4): 319. Patients were randomised into three groups: active treatment, sham treatment, or control (in which bilateral needles were inserted under a shroud). There were marginally significant differences in several measures of efficacy between the active treatment and the control groups post-treatment. For example, the

ETDRS score showed a mean 1.3 line difference post-treatment ( $p = 0.017$ ). These results were sufficiently encouraging for the FDA to sanction a larger Phase III trial, known as MIRA-I, planned to recruit up to 200 patients.

Interestingly, in the FDA pilot study, the sham treatment group fared better than no-treatment (control) group. Reinhard Klingel explained to EuroTimes, “Some large molecular weight complexes adsorb to the tubing and mimic the filter effect to a degree. For this reason, the sham treatment group, in which blood was passed through the tubing but not the filters, was dropped from the MIRA-I study.”

The MIRA-I study was initiated in 1999. The results of an interim analysis of the first 43 patients followed for 12 months were presented at the American Academy of Ophthalmology meeting in 2001, and published in 2002 (*Trans Am Ophthalmol Soc* 2002; 100: 85-107). The findings upheld those from the earlier small controlled trials, albeit again with size limitations.

In the MIRA-I study, patients were randomised to rheopheresis or placebo in a 2:1 ratio, so the first 43 patients comprised 28 rheopheresis- and 15 placebo-controlled patients. Patients were assigned to receive eight rheopheresis or placebo procedures over 10 weeks. All had intermediate- to late-stage dry AMD (approximating to AREDS type 3 and 4 AMD) with multiple soft drusen and elevated serum levels of 2 out of 3 of targeted macromolecules (total serum cholesterol  $\geq 200$  mg/dL; fibrinogen level  $\geq 300$  mg/dL; or serum IgA  $\geq 200$  mg/dL).

The results were comparable with the earlier controlled trials. The mean difference in BCVA was 1.6 lines at 12 months post-baseline, a difference that remained significant throughout the treatment year ( $p = 0.001$ ). Thirteen per cent of rheopheresis eyes, compared with none of the

placebo eyes, gained at least three lines, whereas 4% of rheopheresis compared with 18% of control eyes lost three or more lines in best-corrected visual acuity. The subgroup of patients who had a BCVA of 20/40 or worse at baseline attained a mean difference of three lines at 12 months ( $p = 0.001$ ).

In the subgroup of patients with a BCVA of 20/40 or worse, the authors considered the proportion of patients whose vision improved sufficiently for them to pass a legal driving test (requirement: 20/40 or better); 57.9% of treated eyes passed the test, compared with 14.3% of placebo eyes.

The authors concluded that rheopheresis “demonstrated statistically significant and clinically

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relevant effects on BCVA when compared with placebo controls for the 12-month study interval.” The FDA were sufficiently impressed to make several amendments to the study protocol: the recruitment target was lowered from 180 to 150 patients; the required follow-up was reduced from 12 to six months; and placebo patients were invited to switch to rheopheresis

on completing the study period, enabling them to benefit from rheopheresis.

Nonetheless, the FDA considered 43 patients to be insufficient to give a robust measure of efficacy, and most clinicians, not least the trial investigators themselves, agreed. Despite the positive efficacy of the interim analysis, therefore, the trial continued.

## When is a new treatment ready for patients?

When the MIRA-I interim analysis was presented at the AAO in 2001 there was a tangible sense of excitement: the trial was expected to be completed by the end of 2002 or the beginning of 2003, and marketing approval from the FDA was anticipated by the beginning of 2004. The solid results helped to dispel the scepticism previously felt by many retinal specialists.

But there has now been little news from the trial for two years. Patient recruitment should be completed by December 2004, and so far 130 patients have been enrolled. The 12-month follow-up should be completed by the end of 2005, and FDA approval could come by the end of 2006. So why such a long delay?

“There was brief hiatus due to lack of funding” Dr Boyer told EuroTimes, “But the partnership of OccuLogix with TLC Vision Corporation has fixed that, and we’re progressing well now. We’ve also had some trouble recruiting patients due to the exclusion criteria. They are very rigorous and exclude a lot of elderly people with AMD.”

Dr Klingel was more forthright. “I do think the inclusion criteria of the trial are too restrictive. The problem is not just that the trial is slow to complete recruitment, but also which patients are eligible for treatment afterwards. Should we treat just the same type of patient included in the trial, faithfully reflecting all the exclusion criteria,

or a wider range? If we stick to the trial criteria, are we excluding patients who would benefit?”

Dr Klingel certainly thinks a wider range of patients would benefit. “In Cologne we’re keeping a registry of all patients treated with rheopheresis, which now includes more than 350 patients. Although this is not a controlled study, our findings replicate those of the MIRA-I trial in a broader range of patients. And we must bear in mind that, apart from antioxidants (which our patients received) there is no other treatment for dry AMD. On the basis of these results the largest German medical insurance company, Deutsche Kranken-Versicherung AG, agreed to reimburse for rheopheresis a couple of weeks ago.”

So when is a solid evidence base established? Should patients be treated only within the confines of a clinical trial until efficacy is proven? This is the view of the FDA, and Dr Boyer. Otherwise the potential benefits of innovative treatments like rheopheresis may remain forever at the dubious fringes of clinical medicine.

But one has to share the frustrations of Dr Klingel, and wonder how many patients are losing their sight while clinicians battle through the slow, prosaic reality of clinical trials. At the least, it is time to take rheopheresis for AMD seriously. Should the promising early clinical results be borne out in the long term, debate is sure to follow on related issues such as when and who to treat and whether the cost-benefit ratio is favourable.