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# Clinical studies to implement Rheopheresis for age-related macular degeneration guided by evidence-based-medicine

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## Abstract

In the majority of age-related macular degeneration (AMD) patients the therapeutic situation is very unsatisfactory, especially for patients with dry AMD. Rheopheresis is a safe and effective modality of therapeutic apheresis to treat microcirculatory disorders, and represents a novel therapeutic approach for patients with dry AMD and soft drusen. Elimination of a defined spectrum of high molecular weight proteins from human plasma including pathophysiologically relevant risk factors for AMD such as fibrinogen, LDL-cholesterol,  $\alpha$ 2-macroglobulin, fibronectin, and von-Willebrand factor results in the reduction of blood and plasma viscosity as well as erythrocyte and thrombocyte aggregation. Pulses of lowering blood and plasma viscosity performed as series of Rheopheresis treatments lead to rapid changes of blood flow, subsequently inducing sustained improvement of microcirculation, and recovery of retinal function. Two controlled randomized clinical trials demonstrated safety and efficacy of Rheopheresis for the treatment of AMD patients, especially with the dry form. Recently the interim-analysis of the sham-controlled, double blinded, randomized multicenter MIRA-I trial confirmed these results. The RheoNet-registry and the development and continuous update of therapy guidelines provide an appropriate framework for the quality management of the interdisciplinary cooperation between ophthalmologists with apheresis specialists. A hypothesis based upon current knowledge of pathogenic mechanisms of the development and progression of AMD can be conclusively linked with the putative mechanism of action of Rheopheresis for AMD. A recommendation for high-risk AMD-patients was defined. Based on the positive results of the MIRA-1 interim analysis eight Rheopheresis treatments are currently recommended as the initial treatment series.

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*Keywords:* Therapeutic apheresis; Membrane differential filtration; Rheopheresis; Age related macular degeneration; Dry AMD; Drusen

## 1. Introduction

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible loss of vision and legal blindness in people older than 65 years in

the Western world. In Germany in the year 2000 absolute prevalence of patients between 43 and 86 years with findings of wet AMD was about 430.000, the equivalent prevalence of legally blind AMD patients was about 20.000, accounting for 15–32% of all cases of blindness in Germany [1]. In AMD, progressive damage to the macula results in loss of central vision and affects a person's ability to read, recognize faces, or drive (Fig. 1). AMD

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Fig. 1. Measuring visual acuity with the shown ETDRS reading chart represents the standard parameter to monitor visual acuity in AMD patients within clinical trials. Different charts are used for right and left eye. Results are expressed in lines and characters read by the patient.

can be classified into early and late stages, and occurs in two forms: the non-exudative form (dry AMD) and the exudative form (wet AMD). Clinical manifestations appear as drusen, atrophy of the retinal pigment epithelium (RPE) and choriocapillaris, i.e. dry AMD. RPE detachment, and choroidal neovascularizations (CNV) are characteristic for wet AMD. Patients with wet AMD account for about 25% of total AMD patients [2]. About 80% of severe vision loss caused by AMD is due to the wet form. Patients with only drusen in one or both eyes typically do not have much loss of vision, but they have an increased risk for progression to the late form of the disease and resultant loss of visual acuity (VAC) [3]. Risk factors for that development include number, size and confluence of drusen and abnormal pigment clumping [3,4]. Patients with bilateral soft drusen have a 12.4% risk to develop exudative AMD within 10 years [5]. Patients with exudative AMD in one eye and soft drusen in the fellow eye represent a high-risk group to become legally blind [4]. In summary large numbers of hard drusen predict the incidence of soft drusen and pigmentary abnormalities and that the presence of the latter lesions significantly increases the risk for the development of geographic atrophy and exudative macular degeneration [6].

## 2. Pathogenic mechanisms of AMD—putative links to therapeutic apheresis

The pathogenesis of AMD is not yet fully understood, but a hypothetical sequence of pathogenic events is consistent with known data. Models for AMD pathogenesis include RPE and Bruch's membrane senescence, genetic defects, oxidative insults, ocular perfusion abnormalities, and local inflammatory processes [2,7]. Also functional deterioration of astrocytes in the outer retina have to be discussed as a consequence of changes in retinal microcirculation [8]. Cholesterol, fibrinogen, and  $\alpha$ 2-macroglobulin have been established as risk factors for AMD in epidemiological studies [9–11]. In a controlled cross sectional study patients with dry and wet AMD showed significantly elevated mean levels of vascular endothelial growth factor (VEGF,  $p = 0.019$ ), plasma viscosity ( $p < 0.001$ ), fibrinogen ( $p < 0.001$ ), and von-Willebrand factor (vWF,  $p < 0.001$ ) compared to healthy controls [12]. These results confirm an association between markers of angiogenesis (VEGF), hemorheology (fibrinogen, plasma viscosity), and endothelial dysfunction (vWF) with the pathogenesis of AMD. Molecules associated with local inflammatory processes like IgG, IgA, IgE, C1q, C3 were abundantly detected in subretinal membranes [13].

In the vascular model of Friedman it is hypothesized that lipid deposition in sclera and Bruch’s membrane, a stratified extracellular matrix (ECM) situated between the RPE and choriocapillaris, leads to scleral stiffening and impaired choroidal perfusion, which in turn could adversely affect metabolic transport function of the RPE [14]. The impaired RPE cannot metabolize and transport material shed from the photoreceptors, leading to accumulation of metabolic debris and drusen. This pathogenic model is in accordance with a huge body of findings demonstrated by fluorescein and indocyanine green angiographic methods, laser Doppler flowmetry, and color Doppler imaging [2]. Both choroidal blood flow and choroidal blood volume were about 29% lower in subjects aged 46–76 years compared to subjects aged 15–45 years probably related to a decrease in density and diameter of the choriocapillaris with increasing age [15,16]. In patients with dry AMD and large soft drusen choroidal blood flow and choroidal blood volume were again 37%, 33% respectively lower than in age-matched control subjects. The presence of tissue ischemia and hypoxia in dry AMD may trigger the devel-

opment of angiogenesis with progression to wet AMD (Fig. 2) [15,16]. In patients with bilateral AMD pulsatile ocular blood flow in eyes with drusen was lower than in their fellow eyes with neovascular lesions [17]. These results confirm the clinical risk assessment of soft drusen mentioned above.

Cellular functions of RPE depend upon oxygen concentration [18]. Phagocytosis is a major function of RPE cells and is essential to maintain homeostasis of the microenvironment in the eye. Blood flow can have a direct functional relationship with tissue cells via shear stress. Decreased blood flow could result in decreased RPE phagocytosis by insufficient tissue oxygenation, and reduced induction of TGF- $\beta$  in the vessel wall via reduced shear stress [18–20]. The senescent RPE accumulates metabolic debris as remnants of incomplete degradation from phagocytosed rod and cone membranes. Progressive engorgement of these RPE cells leads to drusen formation with subsequent progressive dysfunction of the remaining RPE. With aging the capacity of Bruch’s membrane to facilitate macromolecular exchange between the choroidal and the RPE compartments

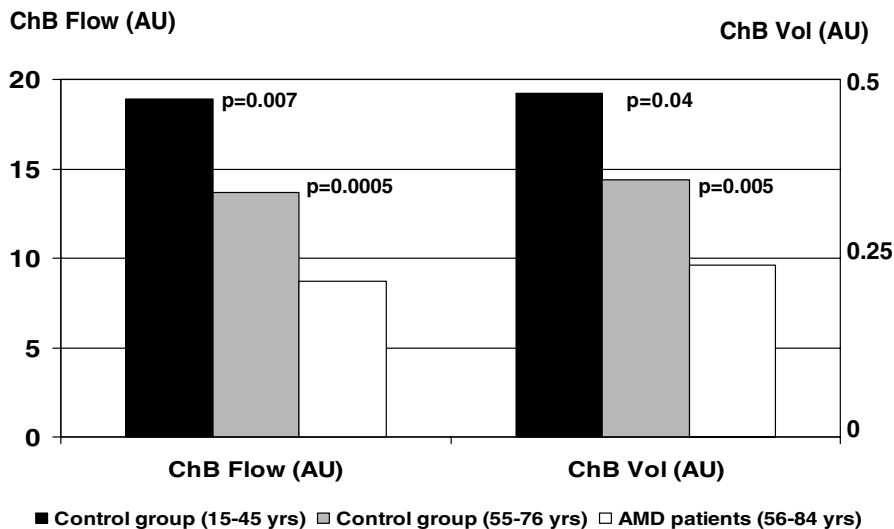


Fig. 2. The effect of aging and AMD on retinal blood flow. The figure shows relative choroidal blood flow (ChB Flow) and volume (ChB Vol) in arbitrary units (AU) in control subjects aged 15–45 years, 55–76 years respectively and AMD patients (56–84 years). Both ChB Flow and ChB Vol were about 29% lower in subjects aged 46–76 years compared to subjects aged 15–45 years. In patients with dry AMD and large soft drusen ChB Flow and ChB Vol were again 37%, 33% respectively lower than in age-matched control subjects (modified from [15,16]).

becomes reduced, representing an important aspect of retinal microcirculation [21,22]. Bruch's membrane thickened with drusen then could facilitate the development of CNV [2].

The macular region including the fovea is an avascular zone, much thinner than the rest of the retina, and receives nourishment by diffusion from the surrounding vasculature and choriocapillaris. Diffusional transport capacities across the Bruch's-choroid complex decline with aging [23]. Angiogenic and antiangiogenic factors in the retina coordinate vascular flow and regeneration with the corresponding metabolic requirements of the retina. Most important are VEGF and pigment epithelium derived factor (PEDF), both regulated by tissue oxygenation [22]. Expression of VEGF is induced by hypoxia, thus promoting neovascularization, PEDF is induced by increase of oxygen, thus inhibiting neovascularization.

The integrity of the vessel wall under quiescent conditions as well as its appropriate responsiveness under conditions of stimulation, inflammation or vascular injury is controlled by a number of adhesive interactions. Two major adhesive proteins relevant for haemostatic mechanisms co-localized in the ECM of the vessel wall have to be mentioned: vWF and vitronectin [24]. By immunohistochemistry and RT-PCR analysis it was shown that vitronectin is a major constituent of human drusen, and that it is expressed by local RPE cells [7]. More common ECM components such as laminin, fibronectin, collagens, and proteoglycans were not detected, indicating, that drusen-associated vitronectin is the result of selective accumulation. Vitronectin is present in high concentrations in plasma and is also common in ECM. Functionally it is related to processes of thrombosis, fibrinolysis, inflammation, and cellular adhesion. Self-association of vitronectin results in the formation of multimeric species of the protein [25]. The balance between monomeric and multimeric forms of vitronectin is important for pathophysiologically relevant changes of ECM sites and fibrinolytic state in plasma [26]. The binding and deposition of vitronectin to Bruch's membrane could compromise the exchange of metabolites between the choriocapillaris and the RPE, eventually leading to RPE and photoreceptor cell

dysfunction and degeneration. RPE cells or by-products of abnormal RPE and/or photoreceptor cell metabolism could serve as nucleation sites for the deposition of proteins such as vitronectin. In a mouse model a vitronectin receptor antagonist could reduce neovascularization in dose-dependent fashion, indicating that vitronectin deposition might be finally a contributing factor of neovascularization [27]. Recent studies implicate inflammation and complement mediated attack as early events in drusen biogenesis. It is likely that RPE cell debris entrapped between the RPE monolayer and Bruch's membrane serves as a chronic inflammatory stimulus and a potential nucleation site for drusen formation [7,28]. Thus, the process of drusen biogenesis may be envisaged as a secondary manifestation of primary RPE pathology that is exacerbated by consequences of local inflammatory processes.

### 3. Therapeutic options for AMD

In the majority of AMD patients the therapeutic situation is very unsatisfactory, especially for patients with dry AMD [2,3]. High-dose supplementation with vitamins C and E, beta carotene, and zinc was recently shown to have some benefit after a 5 year follow-up [29]. Even not all patients with wet AMD are eligible for the following treatment options targeting the different forms of CNV: laser therapy including standard laser photocoagulation, transpupillary thermotherapy (TTT), and photodynamic therapy (PDT), external beam irradiation, and surgical procedures like removal of neovascular membranes or macular rotation. 42% of patients after treatment with PDT showed a letter score loss in the study eye of at least 15 from baseline at the 3 year examination [30]. Laser photocoagulation and TTT are currently tested for dry AMD. However, reports on the occurrence of increased incidence of neovascular lesions after laser photocoagulation or TTT could indicate that both approaches might turn out to be unfavourable for the subsequent course of AMD [31–34]. From a pathophysiological point of view, regarding angiogenic growth factors both treatment modalities seem to induce VEGF rather

than PEDF. In conclusion from the current situation, successful therapy for more subgroups of patients with AMD is urgently needed.

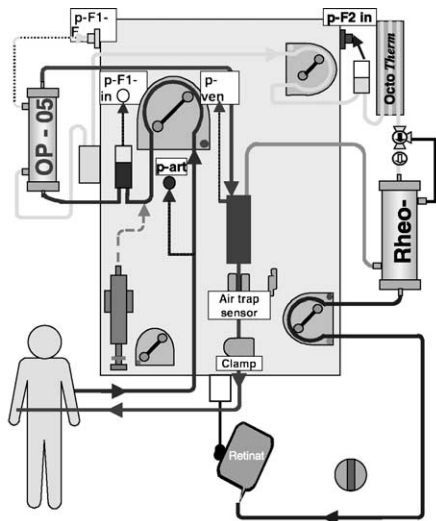
#### 4. Rheopheresis

Rheopheresis is a safe and effective application of membrane differential filtration (MDF, synonymous with double filtration plasmapheresis (DFPP)) for extracorporeal hemorheotherapy (Fig. 3) [35]. The elimination of an exactly defined spectrum of high-molecular weight proteins including fibrinogen,  $\alpha_2$ -macroglobulin, LDL-cholesterol, fibronectin, and vWF results in the reduction of blood and plasma viscosity, erythrocyte and thrombocyte aggregation, and improves erythrocyte flexibility. Pulses of lowering blood and plasma viscosity lead to rapid changes of blood flow, subsequently inducing sustained improvement of microcirculation, which in the eye means recovery of retinal function. In this context microcirculation stands for the complete interactive network between RPE, choriocapillaris, ECM, and blood components. In a pilot trial with eight

patients Rheopheresis accelerated wound healing of foot ulcers of ischemic diabetic foot syndrome and was associated with an improvement of Wagner stage and a pronounced increase in  $tcpO_2$  (Fig. 4) [36]. Values of  $tcpO_2$  remained stable and enhanced for the 3 months follow-up period. As an adjunct therapeutic option Rheopheresis may preserve a functional lower extremity, delay amputation or reduce the extent of amputation. Values of  $tcpO_2$  were still above baseline levels at the 3-month follow-up examination, suggesting a sustained, beneficial effect on tissue oxygenation, which is closely related to tissue function. The achievement of clinically relevant wound healing in 4 out of 8 patients was encouraging. In another pilot trial in patients with diabetic retinopathy, visual function was reported to improve after a series of MDF-treatments [37].

#### 5. Rheopheresis for AMD—clinical trials

Two prospective, controlled, and randomized clinical trials for the treatment of AMD patients with Rheopheresis have been completed, two are



(a)



(b)

Fig. 3. The principle of Rheopheresis (membrane differential filtration/double filtration plasmapheresis with the specifically designed Rheofilter) in a schematic drawing (a) and treatment of an AMD patient in a modern apheresis center using the novel OctoNova technology (b) are shown.



21 weeks. The control group was followed without treatment. Eyes of patients in the therapy and control group both showed CNV in 9/20 eyes, and soft drusen in 11/20 eyes. Comparing initial and final VAC in Rheopheresis and control patients a mean difference of 1.6 EDTRS lines was detected after the treatment series, which was statistically significant with  $p < 0.01$  [38]. Patients with soft drusen and no CNV had the best therapy results. Electrophysiologic investigation of the retina showed significant improvement of photopic  $a$ -wave and the flicker electroretinogram, equivalent to functional improvement of the central photoreceptor complex. Improvement of the pulsatile ocular blood flow and shortening of the arteriovenous passage time in patients with AMD after Rheopheresis treatments was demonstrated earlier (Fig. 6) [40,41].

Thirty patients with dry AMD and soft drusen were included in a three-armed, sham-controlled,

randomized clinical trial conducted at the University of Utah, Salt Lake City. With 10 Rheopheresis treatments 40% of patients showed improvement in at least three out of the following four parameters to assess visual function:  $\geq 2.5$  ETDRS lines best spectacle corrected visual acuity (BSCVAC) in the study eye,  $\geq 2.5$  ETDRS lines in the partner eye, 20% improvement of reading ability in the Pepper visual skills for reading test, and 20% improvement of quality of life tested by the VF14 [39]. In a case series including 10 AMD patients with high-risk AMD and soft drusen improvement of visual acuity essentially identical to the Cologne trial could be confirmed [42]. In fluorescein angiography reduction of soft drusen in number and size was associated with improvement of VAC. However, morphological changes in the retina are not well correlated with VAC also in the natural course of AMD, and should be not considered as the treatment goal [43].

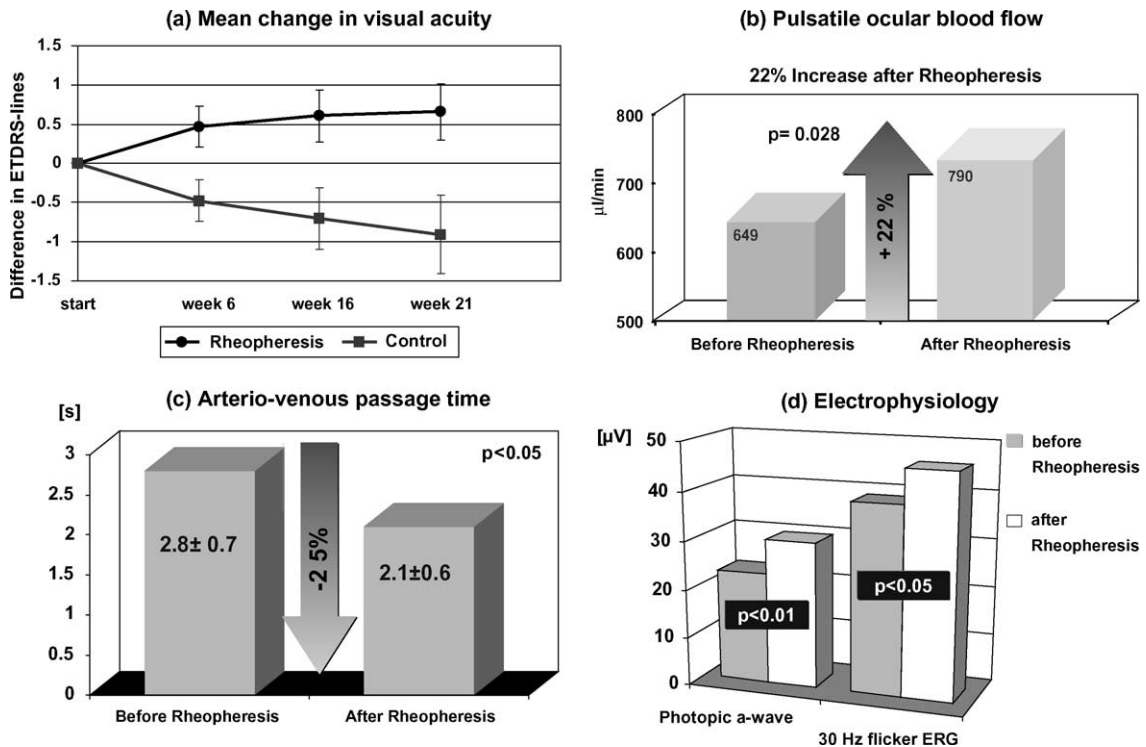


Fig. 6. Parameters which were investigated in clinical trials and demonstrated the positive effect of Rheopheresis in AMD patients: (a) mean change of visual acuity (ETDRS-lines) over time, (b) increase of pulsatile ocular blood flow, (c) decrease of arteriovenous passage time, (d) electrophysiological parameters of retinal function, i.e. photopic  $a$ -wave and 30 Hz flicker ERG (modified from [38,40,41]).

Latest results came from the interim-analysis of the sham-controlled, randomized, multicenter MIRA-1 trial in the US. Repeated measures analysis of 43 patients with preangiogenic dry AMD after a follow-up period of 12 months showed a statistically significant difference between Rheopheresis and control groups, with a mean improvement in VAC of treated patients (R. Klingel, D. Sanders, and J. Pulido for the Writing Committee of the MIRA-1-Study-Group published in *Trans Am Ophthalmol Soc* 2002;100:85–108), aim of the MIRA-1 trial is to evaluate the safety and efficacy of Rheopheresis for the treatment of dry AMD with soft drusen. Hundred and fifty patients are to be randomized in a 2:1 ratio to receive eight Rheopheresis or eight sham-apheresis treatments over 10 weeks and followed for one year. Qualified patients have dry AMD with multiple large soft drusen, to recruit a homogeneous study population defined serum levels of targeted macromolecules, and ETDRS-VAC of 0.16–0.625. In primary eyes the mean ETDRS-line difference at 12 months post baseline between treated and control group was 1.6 lines ( $p = 0.0011$ , repeated measures analysis). The difference was significant throughout the first post-treatment year (Fig. 7). 20% of eyes in the Rheopheresis vs. 9.1% in the placebo group had a  $\geq 2.5$ -line improvement in BCVAC at 12 months post baseline. 4% of Rheopheresis vs. 18.2% of placebo eyes had a  $\geq 3$ -line

loss in BCVAC. Subgroup analysis indicated that eyes with baseline VAC worse than 0.5 derived the greatest treatment benefit at one year with mean difference of 3.0 ETDRS-lines compared to placebo ( $p = 0.001$ ). No severe treatment related adverse events occurred. In a recent reference controlled RheoNet-registry analysis 27 eyes with dry AMD and soft drusen of 18 Patients were evaluated after completion of the initial treatment series in clinical practice. The initial BCVAC was 0.1–0.8. In total 160 Rheopheresis treatments were performed in cooperation with five Rheopheresis competence centers. BCVAC was assessed with ETDRS-charts at baseline and after the treatment series. Patients received in mean 8.8 treatments within 18.3 weeks. Rheopheresis was safe and well tolerated. Compared to baseline ETDRS BCVAC 37% of eyes had a  $\geq 2$ -line, 44% a 1-line improvement. 15% of patients did not change in VAC, 4% had a 1-line, 0% a  $\geq 2$ -line loss. The mean change in VAC was 1.26 ETDRS-lines. In comparison, interim results of the MIRA-1 study revealed 3 months post baseline in 28.6% of treated eyes an improvement of  $\geq 2$ -lines compared to only 6.7% of the eyes in the placebo group. The mean line change was 1.2 at that time. This reference controlled registry analysis is in good accordance with the results of three controlled clinical trials and demonstrates the potential of Rheopheresis as a novel treatment for patients

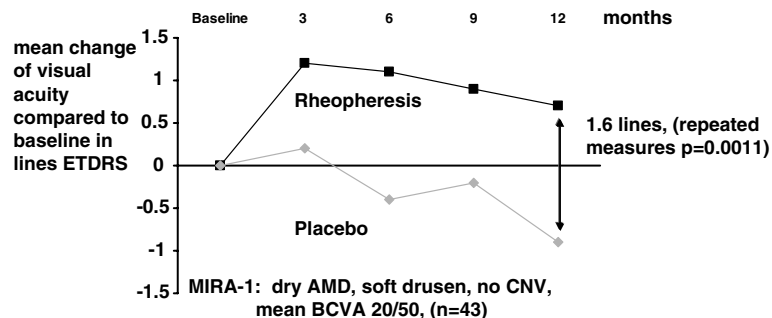


Fig. 7. Interim-results of the controlled, randomized MIRA-1 US multicenter trial evaluating the efficacy of Rheopheresis for the treatment of dry AMD with soft drusen. Mean change in visual acuity (No. of ETDRS-lines) from baseline to the examination at each specified time is depicted. The treatment group received eight Rheopheresis treatments, the control group received a placebo sham apheresis. Repeated measures interim analysis including 43 patients showed a statistically significant difference between both groups at the 12 months follow-up (R. Klingel, D. Sanders, and J. Pulido for the Writing Committee of the MIRA-1-Study-Group published in *Trans Am Ophthalmol Soc* 2002;100:85–108).

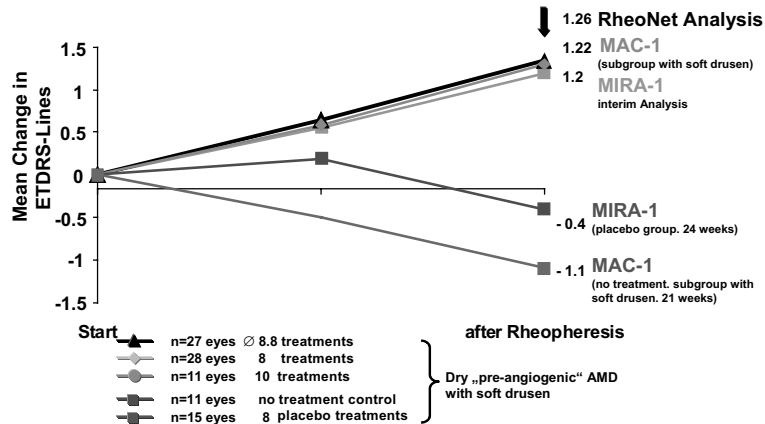


Fig. 8. Reference-controlled RheoNet-registry analysis of 27 eyes with dry AMD and soft drusen. Mean change in visual acuity after the Rheopheresis treatment series in these eyes is compared to corresponding treatment and control groups from the MAC-I trial and interim results of the MIRA-1 trial.

with dry AMD and soft drusen (Fig. 8). From the university of Cologne results of 20 patients were reported after long-term treatment, demonstrating that the therapeutic effect of the initial treatment series can be maintained up to 4 years [44]. Eyes suffering from dry AMD had a mean improvement of visual acuity of 1.9 EDTRS lines after 24 months, 1.2 lines after 36 months, and 0.8 lines after 48 months. After a mean period of 12 months follow-up 2–4 booster treatments could be considered depending upon the individual course [44]. However, these long-term results must be confirmed with larger patient numbers. In summary these data are already appropriate to fulfill *class I*-requirements of the categories of evidence-based-medicine. The final results of the MIRA-1 trial will allow the exact definition for the indication of Rheopheresis in patients with dry AMD.

## 6. Quality management and safety issues: the RheoNet-registry

All methods of extracorporeal blood purification can potentially cause adverse reactions and side effects, which all are well known due to the huge worldwide experience with hemodialysis, plasma exchange, immunoadsorption, and LDL-apheresis. Hypotension, allergic reactions due to blood membrane interactions, hemolysis, or events

associated with anticoagulation have to be mentioned. Anticoagulation for Rheopheresis can be performed with standard and low molecular weight heparin or citric acid. Safety of MDF was analyzed including data from 1702 ambulatory MDF-LDL-apheresis treatments of 52 patients [45]. In 98% of MDF-treatments no adverse reactions occurred. In 2% hypotensive episodes were observed, no severe adverse events occurred [45]. In a trial of Rheopheresis in 10 patients with acute ischemic stroke also no severe adverse events were reported [46]. In the controlled trial of the University of Cologne 20 patients with a mean age of 72 years received a total of 200 Rheopheresis treatments [38]. Hypotension was observed in 6%, hemolysis in 2.5% of treatments. A current RheoNet-registry analysis was performed in December 2002 on the basis of 2021 Rheopheresis treatments in 322 patients, including 207 patients with AMD. Mean age was 66 years (72 years for AMD patients) (Table 1). All adverse events (AE) or side effects, which were caused or associated with Rheopheresis treatments were registered as reported by the German Rheopheresis competence centers. AE were categorized as “reported” (AE-r), or as subgroup “reported and with the need of intervention, temporary break or discontinuation of the treatment” (AE-rI). In 4.65% of treatments AE were reported, but only in 1.19% AE needed intervention, temporary break or discontinuation

Table 1

RheoNet-registry report on adverse events and vascular access problems of 2021 Rheopheresis treatments performed before December 2, 2002 in German Rheopheresis competence centers including 322 patients with a mean age of 66 years (207 AMD patients, mean age 72 years)

	Total reported adverse events/side effects (AE-r)		Reported adverse events/side effects with need of intervention, temporary break or discontinuation (AE-rI)	
	Absolute number	%	Absolute number	%
Hypotension	42	2.08	18	0.89
Hematoma/bleeding	16	0.79	0	0.00
Edema	2	0.10	0	0.00
Dizziness	12	0.59	0	0.00
Eye flickering	2	0.10	0	0.00
Traces of blood in plasma circuit/suspicion of hemolysis (asymptomatic)	4	0.20	3	0.15
Chilling	11	0.54	1	0.05
Fever	1	0.05	1	0.05
Leukocytosis	1	0.05	0	0.00
Retinal bleeding	1	0.05	0	0.00
Headache	1	0.05	0	0.00
Severe intolerance/tetany like symptoms	1	0.05	1	0.05
Total	94	4.65	24	1.19
	Total reported vascular access problems of 2021 Rheopheresis treatments		Reported vascular access problems with need of intervention, temporary break or discontinuation	
Vascular access problems (puncture or flow)	146	7.22	29	1.43

of the treatment. With 0.89% transient hypotension was the most frequent AE of category AE-rI, followed by 0.15% of treatments with detection of traces of blood in the plasma circuit. Hypotension could be controlled in all cases by infusion of saline. No clinical signs of hemolysis were observed. AMD in general has an increased risk of retinal hemorrhage. Only one case of retinal bleeding was reported in an AMD patient 1 day after a Rheopheresis treatment, which caused no irreversible visual impairment. To minimize the bleeding risk citric acid anticoagulation could be used alternative to heparin. Problems with the vascular access (puncture or flow) were reported in 7.22% of treatments, only 1.43% were category AE-rI. Only 1 severe AE-rI (0.05%) was reported in a female patient with sudden deafness, who presented clinical signs equivalent to a severe tetanic reaction, which completely resolved within 24 h after Rheopheresis. Based on interdisciplinary cooperation between ophthalmologists and nephrologists Rhe-

opheresis can be regarded as a very safe ambulatory treatment for elderly patients with AMD.

## 7. Rheopheresis for AMD—mechanism of action

Extracorporeal plasma therapy was not yet used in ophthalmology and therefore requires explanation not only with respect to methodology, but also regarding the mechanism of action. As explained before AMD at cellular and molecular levels is at least in part a microcirculatory disorder of the retina. Therefore it seems to be reasonable to use Rheopheresis, which can successfully treat diseases with impaired microcirculation [35]. It is important for the understanding of the therapeutic potential of Rheopheresis, that the single pulses of plasma protein elimination with associated reduction of plasma viscosity can result in sustained improvements of microcirculation. This of course is a hypothesis, but it is confirmed by available

clinical data for AMD, ischemic diabetic foot syndrome, and fibrinogen/LDL-apheresis for sudden deafness [36,38,47]. Rheopheresis directly targets risk factors and pathophysiologically relevant factors of AMD by lowering plasma viscosity, and eliminating fibrinogen, cholesterol, vWF,  $\alpha$ 2-macroglobulin, and probably multimeric vitronectin. However, these plasma parameters should be regarded as epidemiological risk factors, and not predictive for the individual therapeutic response. A functional reserve exists in the retina affected by AMD, which is determined by the individual pattern of reversible and irreversible morphologic changes of the retina. AMD spontaneously has a chronic progressive course. Irreversible functional and morphologic changes increase over time. The capacity of the individual functional reserve cannot be assessed by any diagnostic procedure. Goal of the Rheopheresis treatment is to restore and activate or stabilize the functional reserve of the retina. The regenerative potential of RPE is well documented in vitro as well as in vivo. But as visual function in general the regenerative potential is highly depending upon microenvironmental conditions, i.e. the degree of morphologic retinal changes and the microcirculatory impairment at cellular and molecular levels. RPE phagocytic function is regulated by tissue oxygen concentration [19]. Rheopheresis treatment results in sustained improvement of tissue oxygenation induced by the repeated therapy pulses, as recently confirmed in a pilot trial in patients with ischemic diabetic foot syndrome [36]. In AMD Rheopheresis could improve RPE phagocytic function directly by the increase of tissue oxygenation, and additionally via shear stress mediated induction of TGF- $\beta$  [18–20]. One of the latest pathogenic pathways described in AMD is the equilibrium shift between the angiogenic growth factor opponents VEGF and PEDF promoting angiogenesis [48]. Rheopheresis could correct this imbalance in favor of inhibition of angiogenesis, resulting in the amelioration of the natural progressive course of AMD. The hypothesis that Rheopheresis might re-balance the angiogenic growth factor systems of VEGF and PEDF is clinically supported by the finding, that also diabetic retinopathy improved from Rheopheresis

treatment [37]. In conclusion, repetitive pulses of plasma protein elimination seem to be capable to change the activity of promoters of the natural course of AMD development and progression. If ophthalmological science has completely elucidated AMD pathogenesis, it will be possible to explain the exact mechanism of action of Rheopheresis for AMD.

## **8. Indication for Rheopheresis in high-risk AMD-patients**

Due to the spreading knowledge about the potential of Rheopheresis numerous AMD-patients wished to become treated unrelated to controlled clinical trials. In total more than 300 patients with AMD have received extracorporeal hemotherapy at the University of Cologne and essentially confirmed the study results in clinical practice (Brunner et al., personal communication). Therefore, a recommendation for high-risk AMD-patients was defined and included in the Apheresis-Guidelines of the German Society for Clinical nephrology, to guarantee that Rheopheresis would be exclusively used for AMD-patients within tight limitations of an interdisciplinary quality management approach [49]. This recommendation for clinical practice will be continuously updated by data from ongoing clinical trials and analysis of the RheoNet-registry to develop complete evidence-based guidelines. The following conditions should be demonstrated to consider Rheopheresis for an individual AMD-patient in clinical practice: (1) bilateral AMD, (2) soft drusen in the better eye, (3) BSCVA 0.1–0.63 of the better eye, (4) exclusion of CNV in the better eye, and (5) Rheopheresis should be complementary and not competitive to other possible therapeutic options for this AMD-patient. Two schedules for 8–10 Rheopheresis treatments were used in the past and seemed to be equally effective. Target for a single treatment is 100% plasma volume. Schedule 1 consists of two Rheopheresis treatments per week, followed by 4-week (MAC-I trial) or 2-week intervals (MIRA-I trial). Schedule 2 consists of two Rheopheresis treatments in the first week, followed by single treatments every two weeks [42]. Based on the

positive results of the MIRA-1-interim-analysis eight single treatments are currently recommended as the initial treatment series.

## 9. Reimbursement issues

Prerequisites exist for acceptance in the medical community, international approval and reimbursement of novel therapies. Safety and efficacy must be assessed by criteria of evidence-based-medicine to ensure that selection and other common sources of bias are minimized. Gold standard for the systematic review of health care is a double-blinded, randomized placebo-controlled clinical trial following Good Clinical Practice guidelines (ICH-GCP) with a publication according to the revised Consort-statement. Within the European community aspects of approval and permission are under law of the European community. But the health care budget must be available in the national health care system, which directs the final decision on reimbursement to national law. Rheopheresis for AMD was first investigated in Germany, therefore the German situation will be considered in the following in more detail. Organisation of the German health care system is currently determined by separation into ambulatory (out-patient) care and in-hospital care. Related to income statutory health insurance is mandatory, currently covering approximately 88% of the German population, the voluntary health insurance system covers approximately 9%. Reimbursement within the statutory health insurance by federal social law depends on the regulations of the National Association of Statutory Health Insurance Physicians (NASHIP). After that decision reimbursement budgets are mainly negotiated between health care authorities and health insurance carriers. Currently lipid-apheresis is the only indication of therapeutic apheresis with regular reimbursement. Reimbursement for Rheopheresis currently depends upon individual application for a single patient. With respect to recent decisions of the German supreme court for social law there is a dilemma. Without a positive decision of NASHIP statutory health insurance carriers are not permitted to reimburse new therapies. On the other hand the supreme court defined

exceptions. If the patient suffers from a morbid condition, which is life threatening or results in a sustained deterioration of quality of life reimbursement is permitted. No alternative treatment must be available and according to available evidence there must be a reasonable expectation for successful therapy. These strained relations characterize the current status of Rheopheresis for AMD in Germany. As a consequence Rheopheresis for AMD is only available for self-paying patients or after successful individual application for reimbursement, which represent pure economic non-medical conditions.

## 10. Conclusion

In the majority of AMD patients the therapeutic situation is very unsatisfactory, especially for patients with dry AMD. Rheopheresis is a safe and effective modality of therapeutic apheresis to treat microcirculatory disorders, and represents a novel therapeutic approach for patients with dry AMD. A series of Rheopheresis treatments with effective pulses of decreased plasma viscosity and elimination of microcirculatory relevant high-molecular weight proteins can induce sustained improvement of the progressive natural course of AMD. The implementation of Rheopheresis into clinical practice is guided by the requirements of evidence-based medicine. However, limitations under the financial constraints of public health care systems increase. The RheoNet-registry and the development and continuous update of therapy guidelines provide an appropriate framework for the quality management of the interdisciplinary cooperation between ophthalmologists with apheresis specialists, namely nephrologists. A hypothesis based upon current knowledge of pathogenic mechanisms of the development and progression of AMD can be conclusively linked with the putative mechanism of action of Rheopheresis for AMD.

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