

Heparin-induced Extracorporeal Lipoprotein Precipitation (HELP) Therapy for Dry AMD

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Although significant recent advances have been made in new therapies for exudative age-related macular degeneration (AMD), no proven therapy exists for reversing the vision loss and pathological retinal changes that occur with dry AMD. Multivitamins, as shown in the AREDS (Age-Related Eye Disease Study),¹ can only reduce the risk of progression of vision loss and pathological macular changes. Novel therapies, such as laser treatment of drusen² and apheresis therapy,³ have not yet proven to be statistically significant in benefit. Slowing the progression of dry AMD, especially if this could reduce the rate of development of exudative AMD, would be of great societal benefit and would have the potential to reduce the significant current costs to health care systems for effective yet very expensive therapies for exudative AMD.

In 2002, the Canada Centre for Advanced Eye Therapeutics (CCAET) in Toronto, Canada, began investigating the use of the Heparin-induced Extracorporeal Lipoprotein Precipitation (HELP) therapy system (B. Braun, Melsungen, Germany) for treating dry AMD. Results of a recently completed clinical study investigating the use of HELP in treating dry AMD were presented at the 8th Euretina Congress in Vienna, Austria in May 2008.

HELP THERAPY SYSTEM

HELP is an established medical therapy first developed more than 20 years ago as treatment for extremely elevated serum cholesterol levels found in familial hyper-



Figure 1. The HELP system unit.

cholesterolemia.⁴ The HELP therapy system was developed by B. Braun Medizintechnologie GmbH, which is a major European medical technology corporation founded more than 100 years ago, specializing in the manufacturing and

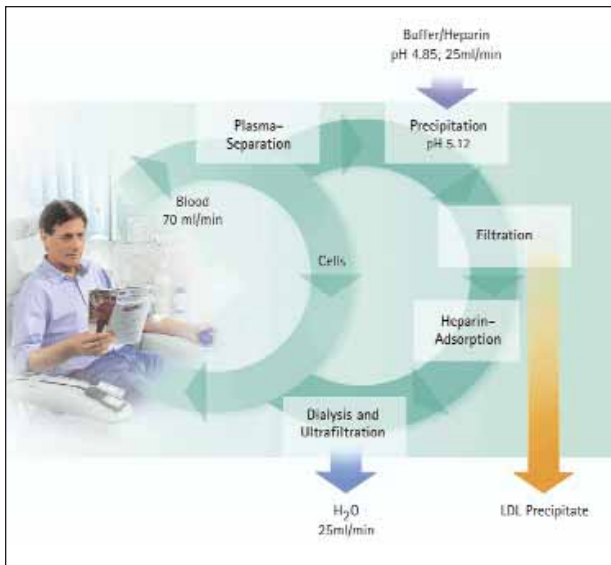


Figure 2. Schematic diagram of HELP process.

marketing of apheresis and dialysis products and systems, as well as surgical instruments and other products. The HELP treatment system is fully approved by the US Food and Drug Administration, Health Protection Branch (Canada), and Communauté Européenne (Europe). HELP has since been demonstrated to be effective in treating other conditions such as: sudden hearing loss,⁵ ischemic optic neuropathy, and coronary artery disease.

The HELP process is derived from the observation that certain plasma proteins, such as lipoproteins, complement factors, and immunoglobulins, will precipitate out of plasma at a given pH level in the presence of heparin.

The HELP treatment system (Figure 1) consists of a self-contained device that removes blood intravenously from the patient, performs the HELP process within the device, and then returns the blood intravenously to the patient. The entire system utilizes sterile, single-use tubing, filters, and chemicals. No foreign blood or blood products are used, and patients undergoing HELP therapy are not given any additional drugs or chemicals as part of the procedure. Several tens of thousands of HELP procedures have been performed worldwide with no incident of serious adverse effects.

For the HELP process itself (Figure 2), the patient's whole blood enters the device via an intravenous catheter inserted temporarily into a peripheral vein. The whole blood is separated into its blood cells and plasma components using a micropore filter. A buffer of specific controlled pH level containing heparin is then mixed with the plasma at a fixed and continuous rate. This initiates the special process in which specific proteins combine with heparin and precipitate out of the plasma solu-

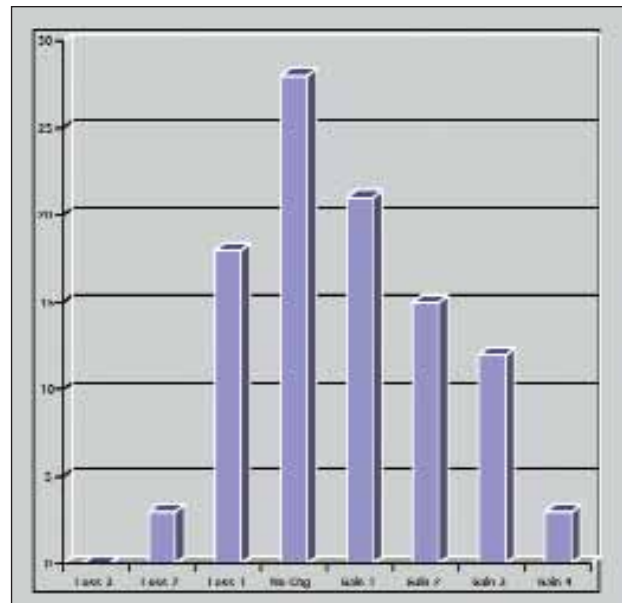


Figure 3. Percentage of patients gaining or losing lines of ETDRS vision.

tion. Protein precipitation occurs in a mixing chamber, and the suspension is passed through a separate micropore filter that removes the precipitated proteins bound to heparin. The remaining heparin is removed using an anion-exchange filter. Bicarbonate dialysis and ultrafiltration is then used to remove the buffer and excess fluid and restore the plasma to a physiologic pH level. The plasma is then recombined with the blood cells and the whole blood is returned to the patient intravenously. HELP is a continuous process that takes 1 to 3 hours and treats a total plasma volume of 1,000 mL to 3,000 mL. However, no more than 500 mL of plasma is ever outside of the patient's body at a given time.

HELP THERAPY FOR DRY AMD

In the prospective study that was presented at the 8th Euretina Congress, 33 qualifying eyes of 19 patients were enrolled. Average patient age was 71.5 years (range 55–87) with 53% female patients. Inclusion criteria included presence of dry AMD with at least one soft drusen and visual acuity $\geq 20/125$ Snellen equivalent. Median baseline visual acuity was 20/68. Mean time between HELP treatment and final follow-up visit was 14.5 months (range 13–19 months).

HELP therapy was performed by specially trained and fully certified apheresis/dialysis technicians and nurses. All HELP procedures, ocular examinations and testing, and follow-up evaluations were performed at the CCAET retina treatment facility.

All patients received eight HELP treatments each per-

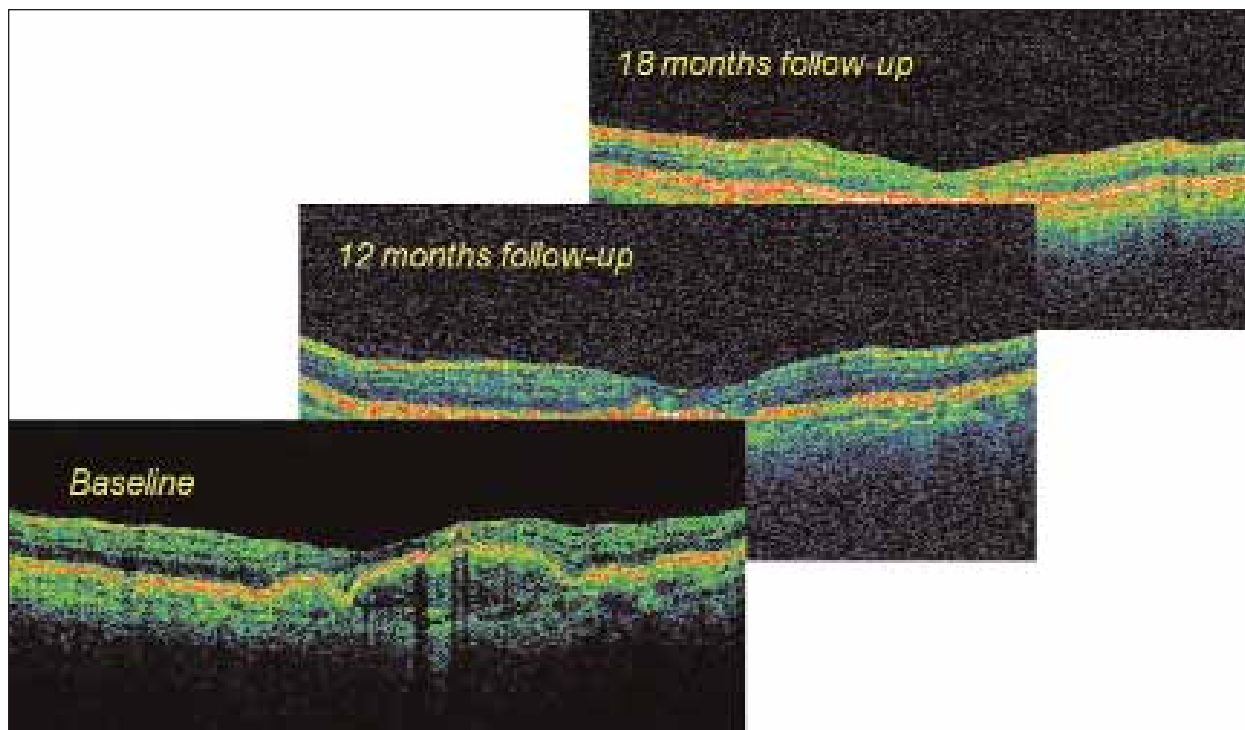


Figure 4. Example of reduction in drusenoid thickening.

formed 7 to 14 days apart. Average total plasma volume treated was 2,684 mL for each HELP session. Ocular outcome measurements included: best-corrected ETDRS visual acuity, contrast sensitivity, optical coherence tomography ([OCT] Stratus 4.0 OCT; Carl Zeiss Meditec, Dublin, CA), microperimetry (MP-1; Nidek, Gamagori, Japan), National Eye Institute Visual Function Questionnaire-25, and fluorescein angiography. Other outcome measurements included evaluation of levels of several key plasma proteins and whole blood viscosity. All outcome measurements were performed at baseline and at regular follow-up visits.

EFFECTS OF HELP ON DRY AMD

All 33 eyes enrolled completed all follow-up assessments. Safety profile was excellent with no serious adverse effects observed.

Visual acuity examination comparing baseline to final assessment visit showed that 15% of eyes improved by three or more lines of ETDRS vision, 0% lost 3 or more lines of vision, and 55% gained at least one line of vision (Figure 3). In addition, 100% (8/8) of eyes with baseline VA of <20/40 regained VA of better than 20/40 at final assessment visit.

OCT exam showed that drusenoid macular thickening, which was present in all eyes, was reduced at final visit in 58% of eyes (Figure 4). Clinical examination also confirmed

reduction in drusen in these patients. The average central macular thickness reduced from 262 μm to 253 μm .

On microperimetry examination, comparing baseline to final assessment visit, 52% of eyes demonstrated improved fixation ability with average fixation stability improving from 79% to 87%.

All patients demonstrated significant reductions in several key plasma protein levels as expected from the known effects of HELP therapy. This included reduction in plasma levels of lipoproteins and inflammatory proteins. Whole blood viscosity levels were also reduced in all patients.

POSSIBLE MECHANISMS OF ACTION

Recent advances in the understanding of probable pathophysiologic mechanisms underlying the development and progression of dry AMD provide possible explanations for the observed clinical effects of HELP therapy on dry AMD. Abnormal activation of immune and inflammatory processes and abnormal accumulation of lipoproteins in the retina are now felt to be critical in dry AMD pathology. HELP is known to have beneficial immunomodulating effects in addition to its great efficacy in lowering plasma lipid levels.

The following processes are now strongly implicated as being involved in the development and progression of dry AMD:

Lipoprotein accumulation causing RPE cell apoptosis.⁶⁻⁷ Lipid accumulates in the retina in part due to breakdown of photoreceptors and the reduced energy needs of the aging eye. Clinical observation has also found elevated serum cholesterol levels to be a risk factor for AMD complications.

Complement activation and immune complex deposition.⁸⁻¹¹ Basal laminar deposits, Bruch's membrane thickening, and drusen formation are all felt to be due to lipid accumulation and inflammatory deposits. Elevated C-reactive protein and homocysteine levels are associated with AMD, and abnormalities of the complement factor H gene are now believed to be a major risk factor for AMD development. Of primary importance may be abnormal activation of complement C3 and C5, and several new therapies for AMD that modify complement activation are currently undergoing clinical trials

Oxidative stress within the retina.¹²⁻¹³ Oxidation of accumulated lipids and carbohydrates in the retina leads to the formation of advanced glycation end products and carboxyethylpyrrole protein adducts. This is believed to be the key step in initiating the abnormal inflammatory response that leads to the development and progression of AMD. Oxidative damage can also lead to microvascular atherosclerosis.

It is significant to note that recognized mechanisms of action and physiological effects of HELP therapy include:¹⁴⁻¹⁶

Significant reduction in lipoprotein levels. HELP therapy results in a very rapid and significant lowering of lipoprotein levels. This allows a more concentrated effect on lipid levels in targeted tissues such as the retina than can be achieved with oral lipid-lowering agents. Lowering retinal lipoprotein levels may interfere with the initiation of the abnormal inflammatory response in AMD as mentioned previously.

Beneficial modification of endothelial inflammation. HELP therapy lowers the levels of inflammatory markers such as C-reactive protein and homocysteine. This is a major advantage of HELP technology over other apheresis systems that filter plasma factors based only on molecular size, as these and other inflammatory markers are too small to be filtered out of plasma by such systems.

Reduction of oxidative stress at cellular level. HELP therapy may be able to slow and even reverse the accumulated effects of oxidative stress over time on the retina. This could explain why only a few HELP therapy sessions could have long term effects on dry AMD: if HELP can in effect "reset" the pathologic retina changes to close to baseline level, then these changes, which took many years to first develop, may not redevelop for many years again after therapy.

Improvement in microvascular circulation. Improved oxygen delivery to the retina may not be as important a benefit as was once thought. However, improved blood flow still would be of possible benefit and may assist in removing waste products and immune complexes from the retina.

CONCLUSIONS

HELP therapy appears to offer the possibility of a safe and effective treatment for dry AMD. It appears reasonable to suggest that the beneficial effects of HELP therapy observed are due to its ability to modify the pathophysiologic processes that lead to the development and progression of dry AMD. Future developments include examining the specific effects HELP therapy has on plasma levels of many of the important inflammatory and immune markers mentioned previously. Additionally, utilizing other ocular outcome measurements, such as high-definition OCT and autofluorescence retinal photography, may increase the understanding of the effects of HELP therapy on dry AMD. ■

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