Effect of Plasmapheresis on Hyperviscosity-Related Retinopathy and Retinal Hemodynamics in Patients with Waldenström's Macroglobulinemia

Marcel N. Menke,[1,2,3] *Gilbert T. Feke,*[1,2] *J. Wallace McMeel,*[1,4] *and Steven P. Treon*[5,6]

PURPOSE. Waldenström's macroglobulinemia (WM) is characterized by an overproduction of immunoglobulin M (IgM), which can lead to a hyperviscosity syndrome (HVS) and HVS-related retinopathy. Plasmapheresis is known to reduce serum viscosity (SV) and IgM levels. The purpose of this study was to investigate the effects of plasmapheresis on HVS-related retinopathy and retinal hemodynamic parameters in patients with WM.

METHODS. Nine patients with HVS due to WM were studied. SV and plasma IgM levels were measured before and after plasmapheresis treatment. The patients were evaluated for HVS-related retinopathy, and hemodynamic changes in a major temporal retinal vein by laser Doppler, before and after plasmapheresis.

RESULTS. Plasmapheresis resulted in significant reductions in serum IgM (46.5% $\pm$ 18.0%, mean $\pm$ SD; $P = 0.0009$) and SV (44.7% $\pm$ 17.3%, $P = 0.002$). HVS-related retinopathy improved in all patients after plasmapheresis. After treatment, the venous diameter decreased in each patient by an average of 15.3% $\pm$ 5.8% ($P = 0.0001$). A significant ($P = 0.0004$) 55.2% $\pm$ 22.5% increase in retinal venous blood speed accompanied the decreases in diameter. There was no significant change in the retinal blood flow rate after treatment. The percentage decreases in SV in the patients were significantly correlated with the percentage decreases in venous blood column diameter ($P = 0.031$, $R^2 = 0.51$).

CONCLUSIONS. HVS triggers a distinctive retinopathy with a central retinal vein occlusion (CRVO)–like appearance. However, the retinal blood flow is not decreased as in CRVO, but remains at normal levels. Plasmapheresis is effective in reversing HVS-related retinopathy and in reducing abnormal venous dilatation. (*Invest Ophthalmol Vis Sci.* 2008;49:1157–1160) DOI: 10.1167/iovs.07-1254

Hyperviscosity syndrome (HVS) is a rare but severe disorder that can accompany monoclonal and occasionally polyclonal paraproteinemias. HVS is especially caused by large molecular compounds with a high intrinsic viscosity such as IgM. Therefore, HVS is most frequent in Waldenström's macroglobulinemia (WM), a rare B-cell disorder characterized by the production of monoclonal IgM.[1,2] Symptoms associated with HVS can be categorized as (1) general symptoms, such as tiredness, fatigue, weight loss, and anorexia; (2) neurologic symptoms, such as dizziness, vertigo, headaches, sudden hearing loss, ataxia, and nausea; and (3) vascular disturbances, such as retinopathy, epistaxis, gingival and gastrointestinal hemorrhages, nephropathy, and congestive heart failure.[3,4]

Historically, the symptoms associated with HVS had been reported to occur at serum viscosity (SV) levels greater than 3 to 4 centipoise (cp).[5,6] The normal range of SV is 1.2 to 1.8 cp. However, our group recently reported[7] that the initial manifestations of HVS-related retinopathy in WM can be seen in the peripheral retina by using indirect ophthalmoscopy with scleral depression in patients with SV levels as low as 2.1 cp and IgM levels as low as 2950 mg/dL. In addition, we demonstrated significant positive correlations between increasing retinal arterial and venous diameters and increasing SV and IgM levels.[7]

Plasmapheresis is the treatment of choice to attain significant reduction of SV levels in patients with HVS. Because IgM is a large molecule that remains 70% to 95% intravascular a single plasmapheresis treatment can result in a reduction in IgM levels of up to 42% with a decrease in SV of 48% to 60%.[8,9] The purpose of this study was to examine the effect of plasmapheresis on HVS-related retinopathy and retinal hemodynamics in patients with HVS due to WM.

METHODS

Nine patients (eight men and one woman, average age 59 $\pm$ 9 years) from the Dana Farber Cancer Institute (DFCI; Boston, MA), who had an established diagnosis of WM, who had been positively tested for HVS, and who were already scheduled for plasmapheresis as part of their treatment regimen at DFCI, were studied.

Plasmapheresis was performed with a commercial system (Spectra Apheresis System; COBE Laboratories, Lakewood, CO).[10] The dual-needle therapeutic plasma exchange (TPE) procedure was used in all patients. During the procedure, anticoagulated whole blood enters the system through an inlet tube. Separation of plasma from the cellular blood components happens in the so-called TPE channel. A built-in centrifuge facilitates the separation of blood components. As blood flows through the TPE channel, cellular components move to the outside of the channel, whereas the plasma remains on the inside of the channel. Most plasma exits the channel through a "plasma-out" tube into a plasma waste bag. The cellular components exit through a separate pathway (the red blood cell return tube), to be returned to the patient. This process ensures that the hematocrit remains unaltered after treatment.

Immediately before plasmapheresis, the patients were evaluated for HVS-related retinopathy. Each patient underwent a visual acuity test,
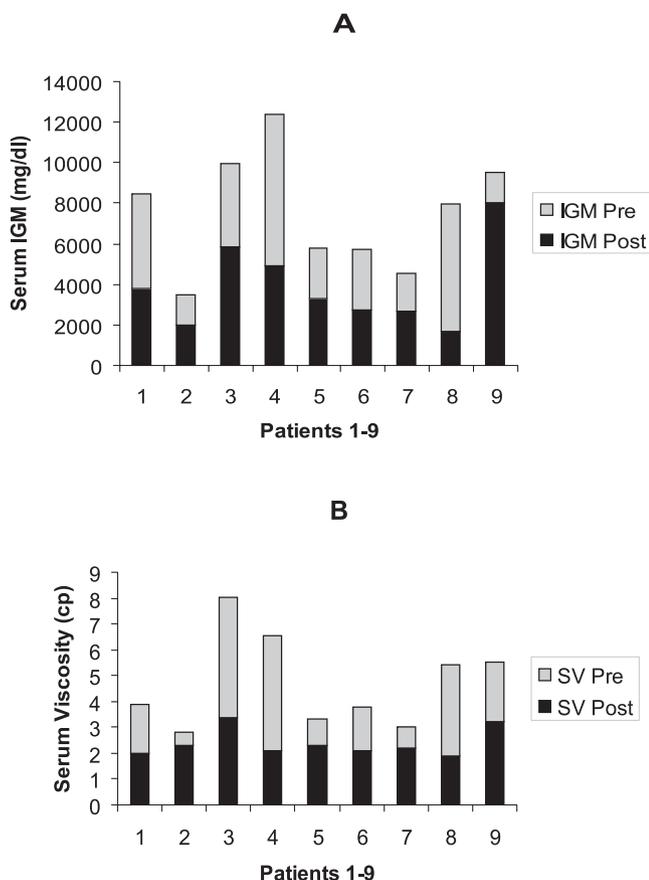
A

B

FIGURE 1. Serum IgM (**A**) and SV (**B**) levels measured in each patient before and after plasmapheresis treatment.

intraocular pressure (IOP) check, slitlamp biomicroscopy, indirect ophthalmoscopy with scleral depression, and fundus photography. In addition, laser Doppler retinal blood flow testing (CLBF 100; Canon, Inc., Tokyo, Japan) was performed in each patient on the major superior or inferior temporal retinal veins in both eyes. Retinal venous blood column diameter and centerline blood speed were measured simultaneously, and the retinal blood flow rate was automatically calculated at each measurement site.[11] The same ophthalmic assessments were repeated between 6 and 22 days after plasmapheresis treatment. Patients remained on the same concomitant medication regimens before and after plasmapheresis.

Follow-up laser Doppler measurement sites along retinal veins were the same as the pretreatment sites. Results from the vein with the largest blood column diameter measured before plasmapheresis in each patient were used in the analysis. Brachial blood pressure, SV, and plasma IgM levels were also measured before and after plasmapheresis. All patients gave written informed consent to undergo the ophthalmic procedures involved in the study and the ophthalmic protocol, approved by the Schepens Eye Research Institute institutional review board, adhered to the guidelines of the Declaration of Helsinki.

The statistical significance of pre- and posttreatment comparisons was assessed with paired *t*-tests. Pearson correlation coefficients between measured variables were determined by simple linear regression analysis. $P < 0.05$ was considered to be statistically significant. Results are expressed as the mean $\pm$ SD.

RESULTS

The serum IgM and SV levels measured in each patient before and after plasmapheresis are shown in Figure 1. The average reduction in serum IgM was 46.5% $\pm$ 18.0% ($P = 0.0009$). The average reduction in SV was 44.7% $\pm$ 17.3% ($P = 0.002$). There were significant decreases in both systolic ($P = 0.0047$) and diastolic ($P = 0.0023$) brachial blood pressures (BP) after plasmapheresis. On average, systolic BP decreased from 127 $\pm$ 17 to 117 $\pm$ 16 mm Hg, and diastolic BP decreased from 65 $\pm$ 13 to 59 $\pm$ 8 mm Hg. Before treatment, average Snellen visual acuity was 20/30 (range, 20/15–20/70), and IOP was 13 $\pm$ 4 mm Hg. There were no significant changes in visual acuity or IOP after plasmapheresis.

Before plasmapheresis, slitlamp biomicroscopy and indirect ophthalmoscopy revealed retinal findings typical in patients with HVS. We found peripheral and central dot and blotlike hemorrhages. Retinal veins were dilated and tortuous, showing focal constrictions, predominantly at arteriovenous junctions (venous sausaging). Optic disc edema was present in two patients. After treatment, retinal appearance improved in all patients, showing narrower retinal veins with less tortuosity, fewer retinal hemorrhages, and decreased optic disc edema, if initially present. Figure 2 shows fundus photographs of a patient before and after plasmapheresis.

The retinal venous blood column diameters measured in each patient before and after plasmapheresis are shown in Figure 3. Before plasmapheresis, the retinal veins were markedly dilated, with an average diameter of 184 $\pm$ 22 μm. After treatment, venous diameters decreased to 155 $\pm$ 18 μm (mean reduction, 15.3% $\pm$ 5.8%, $P = 0.0001$). A significant ($P = 0.0004$) 55.2% $\pm$ 22.5% increase in retinal venous blood speed accompanied the decreases in diameter. Before treatment, venous blood speed was 19.0 $\pm$ 3.3 mm/s; after treatment, blood speed was 29.2 $\pm$ 5.4 mm/s. As a result, there was no significant change in retinal venous blood flow (12.3% $\pm$ 22.0%, $P = 0.16$). On average, the blood flow was 14.2 $\pm$ 4.5 μL/min

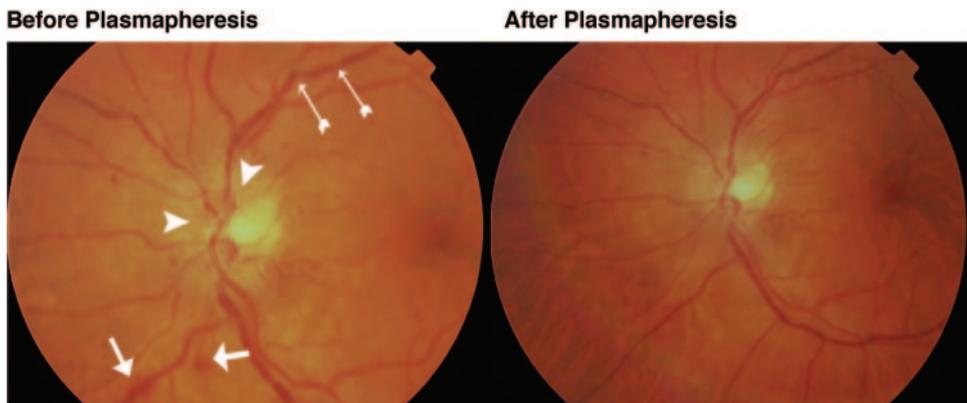**Before Plasmapheresis**   **After Plasmapheresis**

FIGURE 2. *Left:* Before plasmapheresis optic disc edema (*arrowheads*), central retinal hemorrhages (*bold arrows*), and venous "sausaging" (*thin arrows*) were observed. *Right:* After plasmapheresis disc edema and retinal hemorrhages improved. Venous sausaging disappeared.

before treatment and 15.8 ± 5.7 μL/min after treatment. As shown in Figure 4, the percentage decreases in SV after plasmapheresis correlated significantly with the accompanying percentage deceases in retinal venous diameter ($P = 0.031$, $R^2 = 0.51$).

DISCUSSION

Our patients showed significant reductions in SV and serum IgM levels after plasmapheresis treatment. These reductions were accompanied by a lessening of the severity of HVS-related retinopathy. Our findings are in agreement with those in early studies,[12,13] showing that plasmapheresis is effective in reversing HVS-related retinopathy in patients with WM.

The hemodynamic measurements showed significant reductions in venous diameter that were accompanied by significant increases in venous blood speed after plasmapheresis. As a result, the blood flow rate after treatment was not significantly different from the pretreatment level. It is possible, however, that the 11% increase in blood flow rate measured after treatment may have been due to an underestimation of the blood speed before treatment. The calculation of the blood flow rate assumes a parabolic spatial profile of blood speeds in the measured vessel.[11] The elevated SV present before treatment may have produced some blunting of the speed profile. After treatment, with reduced SV, the profile most likely reverted to its parabolic shape.

Other investigators[14,15] had used video fluorescein angiography to investigate the retinal circulation in patients with HVS and found abnormally long arteriovenous passage times of the dye tracer. This suggested a reduced blood speed in these patients and perpetuated the supposition[16] that HVS is a type of venous stasis retinopathy that is also found in central retinal vein occlusion. The results of our recently reported cross-sectional study,[7] however, showed that while dilated retinal vessels and reduced blood speeds are indicative of HVS-related retinopathy, the blood flow rate itself remains at a healthy normal level. The results of our present study, reported herein, also show that the blood flow rate remains essentially unchanged during the reversal of HVS-related retinopathy.

Moreover, our results showed a significant correlation between the percentage decrease in SV levels and the percentage decrease in retinal venous diameters after plasmapheresis. This coupling between SV levels and retinal vessel diameters was also shown in our prior study.[7] Elevated SV increases the vascular resistance to flow, whereas vascular dilatation decreases the resistance to flow. It appears that the retinal vas-
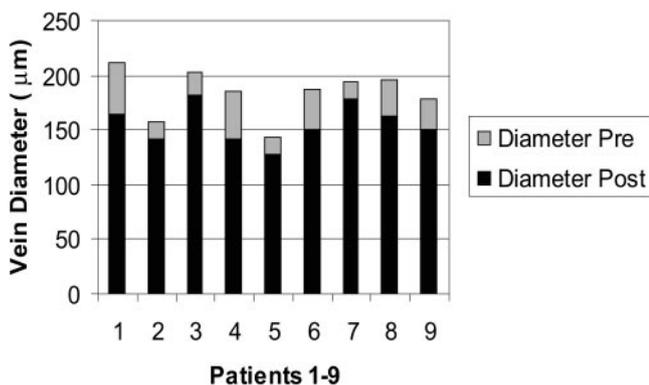

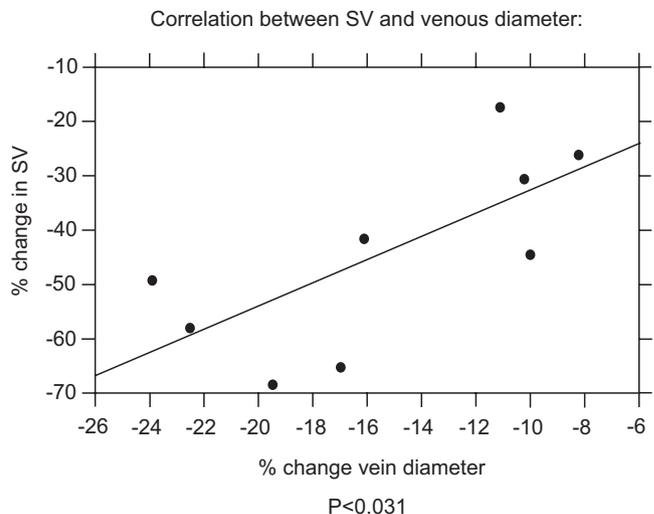Correlation between SV and venous diameter:

FIGURE 4. Regression plot showing the correlation between the percentage change in serum viscosity and the percentage change in retinal venous diameter after plasmapheresis treatment.

cular response to plasmapheresis is a vascular constriction of just the appropriate magnitude to balance the change in resistance caused by the decrease in SV. This result suggests that the hemodynamic results that we have observed in patients with WM and HVS are governed by a well functioning retinal vascular autoregulation system.[17]

As we have suggested,[7] in HVS, there is an active compensatory arterial and arteriolar dilation that results in higher local intravascular pressures throughout the capillary network that explains the occurrence of retinal hemorrhages. The elevated pressures extend to the venous side of the vascular system and explain the observed venous dilation.

A contributing factor to the observed venous dilation may be hypervolemia, which frequently accompanies HVS.[18] Plasmapheresis is known to reduce hypervolemia.[19] The significant decrease in the systolic and diastolic brachial blood pressures after plasmapheresis may be related to the reduction in hypervolemia.

In summary, hyperviscosity triggers a particular type of retinopathy with retinal vein occlusion–like appearance. However, retinal blood flow remains at normal levels. Plasmapheresis ameliorates HVS-related retinopathy and normalizes retinal hemodynamics. Examination of the retina is useful in identifying the symptomatic threshold of plasma viscosity levels in patients with HVS and can be used to gauge the effectiveness of plasmapheresis treatment.

References

1. Dimopoulos MA, Panayiotidis P, Moulopoulos LA, Sfikakis P, Dalakas M. Waldenström's macroglobulinemia: clinical features, complications, and management. *J Clin Oncol.* 2000;18(1):214–226.

2. Johnson SA. Waldenström's macroglobulinemia. *Rev Clin Exp Hematol.* 2002;6(4):421–434.

3. Dimopoulos MA, Kyle RA, Anagnostopoulos A, Treon SP. Diagnosis and management of Waldenström's macroglobulinemia. *J Clin Oncol.* 2005;23(7):1564–1577.

4. Menke MN, Treon SP. Hyperviscosity syndrome. In: Sekeres MA, Kalaycio ME, Bolwell BJ, eds. *Clinical Malignant Hemotology.* New York: McGraw Hill; 2007:937–941.

FIGURE 3. Bar chart showing the retinal venous blood column diameter measured in each patient before and after plasmapheresis treatment.

5. Fahey JL, Barth WF, Solomon A. Serum hyperviscosity syndrome. *JAMA*. 1965;192(5):464–467.

6. Crawford J, Cox EB, Cohen HJ. Evaluation of hyperviscosity in monoclonal gammopathies. *Am J Med*. 1985;79(1):13–22.

7. Menke MN, Feke GT, McMeel JW, Branagan A, Hunter Z, Treon SP. Hyperviscosity-related retinopathy in Waldenström macroglobulinemia. *Arch Ophthalmol*. 2006;124(11):1601–1606.

8. Reinhart WH, Lutolf O, Nydegger UR, Mahler F, Straub PW. Plasmapheresis for hyperviscosity syndrome in macroglobulinemia Waldenström and multiple myeloma: influence on blood rheology and the microcirculation. *J Lab Clin Med*. 1992;119(1):69–76.

9. Hoffkes HG, Heemann UW, Teschendorf C, Uppenkamp M, Philipp T. Hyperviscosity syndrome: efficacy and comparison of plasma exchange by plasma separation and cascade filtration in patients with immunocytoma of Waldenström's type. *Clin Nephrol*. 1995;43(5):335–338.

10. Koo AP. Overview of therapeutic apheresis in the USA. *Ther Apher*. 1999;3(1):4–7.

11. Yoshida A, Feke GT, Mori F, et al. Reproducibility and clinical application of a newly developed stabilized retinal laser Doppler instrument. *Am J Ophthalmol*. 2003;135(3):356–361.

12. Schwab PJ, Okun E, Fahey JL. Reversal of retinopathy in Waldenström's macroglobulinemia by plasmapheresis: a report of two cases. *Arch Ophthalmol*. 1960;64(10):515–521.

13. Ackerman AL. The ocular manifestations of Waldenström's macroglobulinemia and its treatment. *Arch Ophthalmol*. 1962;67(6):701–707.

14. Knabben H, Wolf S, Remky A, Schulte K, Arend O, Reim M. Retinal hemodynamics in patients with hyperviscosity syndrome. *Klin Monatsbl Augenheilkd*. 1995;206(3):152–156.

15. Dobberstein H, Solbach U, Weinberger A, Wolf S. Correlation between retinal microcirculation and blood viscosity in patients with hyperviscosity syndrome. *Clin Hemorheol Microcirc*. 1999;20(1):31–35.

16. Feman SS, Stein RS. Waldenström's macroglobulinemia, a hyperviscosity manifestation of venous stasis retinopathy. *Int Ophthalmol*. 1981;4(1–2):107–112.

17. Alm A. Ocular circulation. In: Hart WM, ed. *Adler's Physiology of the Eye*. St. Louis: Mosby; 1992:198–227.

18. Russell JA, Powles RL. The relationship between serum viscosity, hypervolaemia and clinical manifestations associated with circulating paraprotein. *Br J Haematol*. 1978;39(2):163–175.

19. Euler HH, Schmitz N, Löffler H. Plasmapheresis in paraproteinemia (in German). *Blut*. 1985;50(6):321–330.