

# Intensive, Long-Term Plasma Exchange Therapy for Severe Hypertriglyceridemia in Acquired Generalized Lipoatrophy

CHARLES BOLAN\*, ELIF ARIOGLU ORAL\*, PHILLIP GORDEN, SIMEON TAYLOR, AND SUSAN F. LEITMAN

*Department of Transfusion Medicine, Warren Magnuson Clinical Center (C.B., S.F.L.), and Diabetes Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (E.A.O., P.G., S.T.), Bethesda, Maryland 20892; and Walter Reed Army Institute of Research (C.B.), Silver Spring, Maryland 20910*

**We report dramatic improvement in clinical and laboratory parameters after intensive plasma exchange therapy in a 15-yr-old girl with acquired generalized lipoatrophy and refractory hypertriglyceridemia. One hundred and twenty-five procedures were performed over 720 d. Two or three plasma volumes were exchanged per procedure, using peripheral venous access and albumin as replacement solution. Regression of painful cutaneous xanthomata and reduction in massive hepatomegaly were noted within the first two procedures. Triglyceride levels started at 109 mmol/liter (9670 mg/dl) and decreased acutely by 60–85%/procedure. Lipid removal averaged 83 g/procedure and was highly correlated with preexchange lipid levels. Lipid levels rebounded to baseline values**

**within 7 d after exchange and appeared to rebound more rapidly after larger exchanges. Maximum benefit was achieved with weekly 1.5- to 2.0-volume exchanges. No significant decrease in apolipoprotein CII levels was detected after plasma exchange regardless of the volume of exchange; however, other plasma factors regulating triglyceride synthesis or clearance may have been removed during the procedures. Plasma exchange was well tolerated, without clinical, immunological, or hormonal deterioration. These data indicate that intensive plasma exchange therapy over a protracted time may produce sustained benefit in patients with severe, symptomatic hypertriglyceridemia refractory to standard medical therapy. (*J Clin Endocrinol Metab* 87: 380–384, 2002)**

**A**QUIRED GENERALIZED lipoatrophy is a rare condition characterized by a paucity of fat along with insulin-resistant diabetes and hypertriglyceridemia (1). The molecular mechanisms leading to fat loss are unknown. Recent evidence suggests that the absence of fat is the primary event that leads to the associated metabolic abnormalities (2). Hypertriglyceridemia may be profound, leading to visceral organomegaly and pancreatitis. Rarely, cutaneous xanthomata may be observed in cases with extreme elevations in triglyceride levels (3). In this report we describe the use of intensive, long-term plasma exchange to ameliorate symptoms in a 15-yr-old girl with acquired generalized lipoatrophy and hypertriglyceridemia refractory to lipid-lowering agents, in whom other therapies were either contraindicated or ineffective.

## Subjects and Methods

### Case presentation

The patient first presented at age 12 yr with eruptive xanthomas and a blood triglyceride level of 181 mmol/liter (16,000 mg/dl). Review of pictures from birth showed a normal amount of facial fat in infancy, which decreased progressively until the time of presentation (Fig. 1). The mother had a normal lipid profile, with a body mass index of 34 kg/m<sup>2</sup>. The father had an abnormal lipid profile and body habitus similar to the patient's at age 6 yr. The patient's developmental milestones were normal. She underwent menarche at age 12 yr, but was amenorrheic after age 14 yr. Triglyceride levels and xanthomata were initially responsive to diet, exercise, and administration of lipid-lowering agents (Table 1). However, blood lipid levels, hepatomegaly, and painful xanthomas progressed as her visible body fat decreased further, from age 14–15 yr. She was referred to our facility for evaluation as a participant in a clinical trial testing the efficacy of troglitazone in lipoatrophic diabetes (4).

Medications on referral included atorvastatin, fenofibrate, metformin, and acarbose (Table 1). The patient was advised to follow a low fat (<20%) diet, which was a particularly difficult goal to achieve due to the increased appetite that is observed in patients with generalized lipoatrophy.

On referral, the patient was an intelligent girl with emaciated-appearing facies and extremities, a tensely protuberant abdomen, and exuberant eruptive xanthomas covering the face, trunk, extremities, palms, and soles. Acral xanthomas had surrounding erythema and were exquisitely painful, limiting hand-grip and ambulation. Fundoscopic examination revealed milky infiltrates on the retina. There was no adenopathy. The heart and lungs were normal. The liver edge extended into the pelvic brim. There was no evidence of ascites, and the spleen was not palpable. Her weight was 32 kg.

Laboratory values included triglycerides of 109 mmol/liter (9679 mg/dl; normal, 30–155 mg/dl or 0.3–1.8 mmol/liter), total cholesterol of 253 mmol/liter (978 mg/dl; normal, <200 mg/dl or < 5.2 mmol/liter), and high density lipoprotein cholesterol of 0.54 mmol/liter (21 mg/dl; normal, >35 mg/dl or >0.9 mmol/liter). Lipoprotein electrophoresis revealed a markedly elevated very low density lipoprotein fraction. All other laboratory tests were performed on ultracentrifuged samples. The complete blood count was normal, Serum creatinine was 35.4 μmol/liter (0.4 mg/dl), fasting glucose was 8.88 mmol/liter (160 mg/dl), and hemoglobin A<sub>1c</sub> was 9% (normal, 4.4–6.2%). Alanine and aspartate aminotransferase levels ranged from 62–98 U/liter (normal, <41 U/liter and <35 U/liter, respectively), whereas alkaline phosphatase and total bilirubin were normal. Serum total protein and albumin levels were normal. Fasting insulin levels were elevated at 579 pmol/liter (80.7 μU/ml; normal, 4–20 μU/ml or 36–179 pmol/liter), and C peptide levels were increased at 4.9 μg/liter (normal range, 0.5–2.0 μg/liter). Twenty-four-hour urinary protein excretion varied between 4–9 g daily. A dual energy x-ray absorptiometry scan indicated 7% body fat (minimum on this technique), and the plasma leptin concentration was below the detection limit (<1 ng/ml).

Liver biopsy revealed steatosis and early cirrhosis. Renal biopsy showed renal tubular lipidosis and early focal glomerular sclerosis.

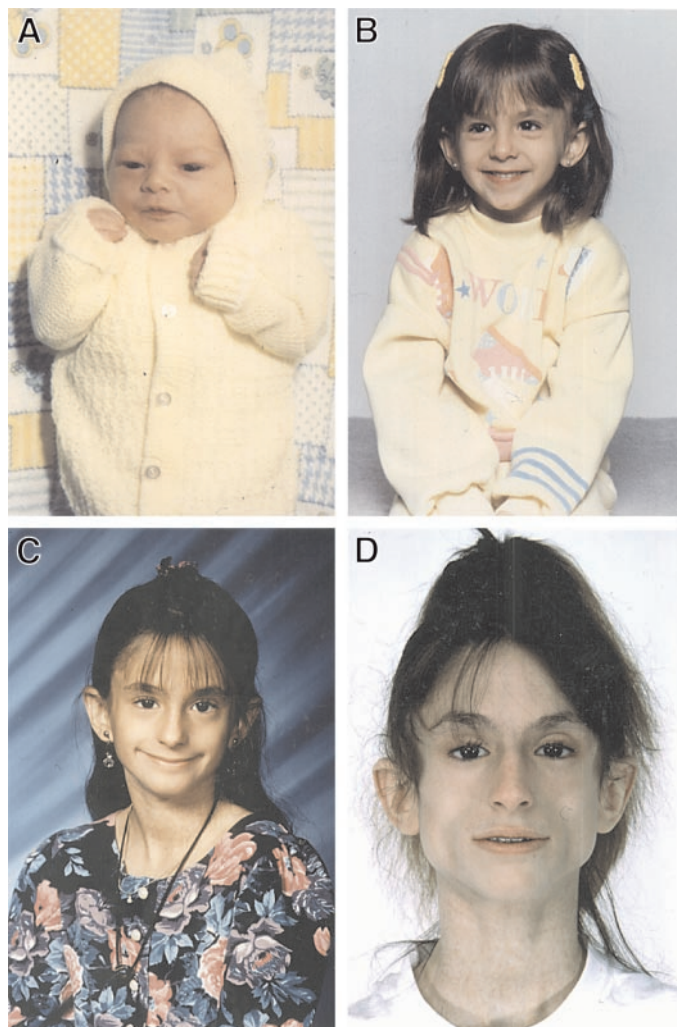


FIG. 1. Progressive fat loss in index patient with acquired generalized lipoatrophy at age 6 months (A), 5.5 yr (B), 11.5 yr (C), and 15 yr (D).

Magnetic resonance imaging of the abdomen and limb muscles demonstrated massive hepatomegaly and complete absence of body fat, except bone marrow fat. Due to the degree of hepatic impairment, she was ineligible for participation in the troglitazone trial.

#### Plasma exchange therapy

As conventional lipid-lowering agents were ineffective (Table 1), and investigational agents were unavailable, we initiated a trial of plasma exchange therapy in an attempt to reduce the debilitating effects of the patient's excess plasma lipids by physical means. Procedures were performed using continuous flow centrifugation (Spectra Apheresis System, Cobe, Lakewood, CO) with bilateral antecubital venous access. Topical 2.5% lidocaine and 2.5% prilocaine cream (EMLA, Astra USA, Inc., Wayne, PA) were applied to the antecubital areas 1 h before venipuncture. The apheresis device interface detector was disabled during the initial few procedures, as the milky turbidity of the plasma prevented the optical sensor from detecting the interface that formed between the packed red cells and plasma during centrifugation. Citrate (ACD Formula A, Baxter Healthcare, Deerfield, IL) was used as an anticoagulant at an ACD-A to whole blood ratio of 1:13, and replacement was made with a 4% albumin solution. The volume of exchange ranged from 2–3 plasma volumes, or 2800–4200 ml/procedure (the volume of exchange is defined as the volume of plasma removed). The first 30 procedures were performed without calcium supplementation. Subsequently, calcium chloride was given by continuous iv infusion through the return

line of the apheresis harness, at a rate of 0.3 mg calcium/ml ACD-A-min (5). The whole blood flow rate ranged from 40–50 ml/min in procedures performed without prophylactic calcium to 60–80 ml/min in those with calcium.

## Results

#### Effect of plasma exchange on cutaneous xanthomas

Plasma exchange was initiated at weekly intervals and accelerated to twice weekly during a 3-month period encompassing procedures 8–36. Thereafter, the procedures were performed weekly. A total of 125 procedures were performed over 720 d (Fig. 2). After the second exchange, the patient reported significant softening and regression of skin xanthomas and was able for the first time in months to walk barefoot on a hard floor. After four exchanges, she was able to use her fingers to write, to groom and dress herself, to turn a water faucet, and to hold kitchen utensils. With continued intensive apheresis, conducted at semiweekly to weekly intervals for the next 18 months, she reported complete regression of facial xanthomas, nearly complete regression of xanthomas on arms and legs, and sufficient reduction in size and tenderness of xanthomas on her fingers to allow her to resume playing the piano (Fig. 3). The erythema surrounding the digital, palmar, and plantar xanthomas resolved completely. Her appetite and weight did not change significantly during the course of intensive exchange.

Maximum diminution in the size of the cutaneous xanthomas was attained after approximately 40 procedures. Continued exchange on a weekly basis sustained these effects; however, prolongation of the interval between successive exchanges to 2 wk or more due to vacation or travel was accompanied by visible regrowth of tender acral xanthomas. Episodes of more than usual deviation from her diet and periods of exacerbation of seasonal asthma, requiring steroid therapy, were also associated with recurrent pain and rapid regrowth of cutaneous xanthomata.

#### Effect of plasma exchange on liver function and size

Each plasma exchange lowered serum transaminase concentrations by  $36 \pm 12\%$  acutely, as expected. The levels returned to prepheresis levels within the course of the next 48 h, as noted within the first 2 wk of in-patient therapy. The prepheresis plasma transaminase concentrations slowly improved over the course of the first 40 procedures. The nadir prepheresis serum alanine and aspartate transaminase concentrations were 26 and 16 IU/liter, respectively. The patient's liver volume, as determined by magnetic resonance imaging at presentation, was 6905 ml, and liver volume 1 yr later was 5178 ml, indicating a 25% reduction.

#### Effect of plasma exchange on lipid and glucose control parameters

Plasma exchange was accompanied by an acute 60–85% reduction in circulating triglyceride, total cholesterol, low and high density lipoprotein cholesterol levels, with the degree of the reduction strongly related to the volume of exchange. The pace of lipid rebound was difficult to evaluate, because even modest episodes of dietary indiscretion could rapidly and dramatically raise serum triglyceride levels. In general, triglyceride levels rose to

**TABLE 1.** Course of evolution of hyperlipidemia in the patient with acquired generalized lipoatrophy

Age (yr)	Glucose (mmol/liter)	Triglycerides (mmol/liter)	Medical intervention
12	Normal	181	Low-fat diet, exercise, gemfibrozil 300 mg BID
12 <sup>6/12</sup>	Normal	44	Low-fat diet, exercise, gemfibrozil 300 mg BID
14 <sup>6/12</sup>	13.9	139	Low-fat diet, exercise, gemfibrozil 600 mg BID
15	9.7	124	Low-fat diet, fenofibrate 225 mg QD, metformin 500 mg BID, acarbose 100 mg TID
15 <sup>3/12</sup>	10.7	99	Low-fat diet, fenofibrate 225 mg QD, atorvastatin 10 mg QD, metformin 500 mg BID, acarbose 100 mg TID
15 <sup>4/12</sup>	12.3	109–132	NIH-referral, initiation of plasma exchange therapy

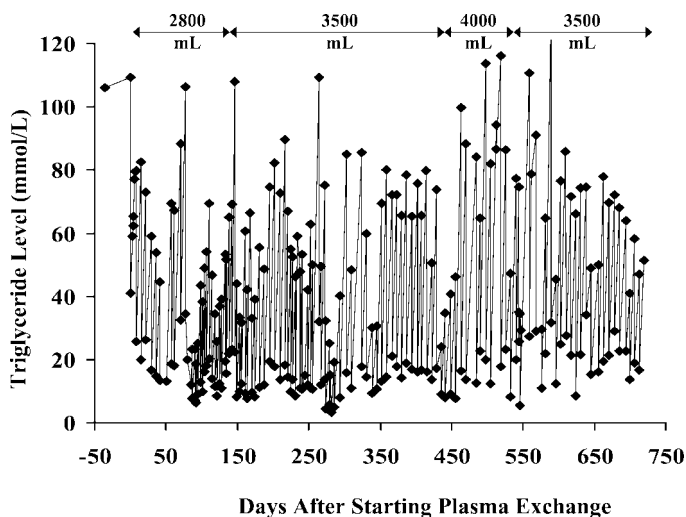


FIG. 2. Plasma triglyceride levels in millimoles per liter (normal, 0.3–1.8 mmol/liter or 30–155 mg/dl) during plasma exchange therapy. The volume of exchange was manipulated as follows: procedures 1–28, 2800 ml (two plasma volumes); procedures 29–83, 3500 ml (2.5 plasma volumes); procedures 84–97, 4000 ml (2.8 plasma volumes); and procedures 98–125, 3500 ml. Lipid levels appeared to rebound more rapidly after large (2.8-volume) procedures.

preapheresis values within 7 d (Fig. 2). Rebound in lipid levels tended to occur more quickly after larger volume procedures, averaging  $10 \pm 3.2$  mmol/liter-d ( $893 \pm 283$  mg/dl) after 4200 ml,  $8.0 \pm 4.6$  mmol/liter-d ( $709 \pm 407$  mg/dl) after 3600 ml, and  $8.1 \pm 3.8$  mmol/liter-d ( $717 \pm 337$  mg/dl) after 3000 ml procedures; however, these differences were not statistically significant. Marked increases in plasma triglycerides were also observed during periods of dietary indiscretion, during an exacerbation of asthma treated with oral steroids, and when the interval between consecutive exchanges was greater than 1 wk.

The estimated volume of distribution for triglycerides, computed from the change in pre- to postapheresis blood levels and the lipid content in the bag of plasma removed with each procedure, was 2.2 liters, or 1.5 plasma volume, consistent with extracellular distribution of triglycerides (6). The total lipid content removed with each procedure, computed from the volume and lipid concentration of the apheresis plasma bag, ranged from 24–237 g/procedure (mean, 83 g) and was highly correlated with preapheresis blood triglyceride levels ( $r^2 = 0.85$ ;  $P < 0.0001$ ). Over the course of this report, 11.1 kg triglycerides and cholesterol were removed during apheresis.

As expected, circulating FFA levels decreased with each procedure. Data collected during the first five procedures

indicated a mean prepheresis level of  $1873 \pm 1619$   $\mu$ mol/liter and a mean postpheresis level of  $1710 \pm 423$   $\mu$ mol/liter. Apolipoprotein CII levels did not decrease after apheresis.

The patient's hemoglobin A<sub>1c</sub> at presentation was 9.6%, and this was lowered to 8.6% within the first 40 procedures and was maintained between 8.3–8.8% for the remainder of the study. During the course of therapy, fasting insulin levels decreased from  $81 \pm 20$  to  $47 \pm 14$   $\mu$ U/ml ( $581 \pm 143$  to  $337 \pm 100$  pmol/liter), and C peptide levels fell from  $4.9 \pm 1.2$  to  $3.4 \pm 0.9$   $\mu$ g/liter (or ng/ml).

#### Adverse effects of intensive exchange

The apheresis procedures were generally well tolerated. Vasovagal symptoms, with lightheadedness and nausea, occurred near the completion of larger volume exchanges (>2.5 plasma volume processed) and could be reduced by saline infusions (10 ml/kg over 20 min) before the procedure. During two procedures, the patient developed fever, flushing, and abdominal pain near the end of the exchange. Blood cultures were negative, and she recovered within 12 h. These symptoms did not recur when the albumin replacement solution was changed to a different lot.

Ionized calcium levels decreased by 10–20%/procedure in the absence of calcium replacement. Prophylactic use of continuous iv calcium chloride infusions, administered in a fixed ratio with ACD-A, resulted in preservation of higher ionized calcium levels, allowed the procedures to be performed at higher whole blood flow rates (decreasing the duration of the procedure), and was associated with an improvement in postapheresis nausea and fatigue.

Fibrinogen levels decreased by 75%, and prothrombin and partial thromboplastin times increased by 6 and 9 sec, respectively, when measured immediately after two-volume exchanges. These changes were transient, however, and no bleeding episodes occurred. Serum Ig levels decreased by 60–80% with each procedure. The nadir preapheresis IgG level was 167 mg/dl on d 490, after 10 weekly 2.8-volume exchanges. The patient experienced a seasonal exacerbation of previously diagnosed asthma, but did not experience any infections or other clinical evidence of immune dysfunction or impairment during the course of plasma exchange therapy.

#### Discussion

This is the first report of the use of long-term, intensive plasma exchange therapy for treatment of severe hypertriglyceridemia associated with acquired generalized lipoatrophy. Although hypertriglyceridemia commonly accompanies lipodys-

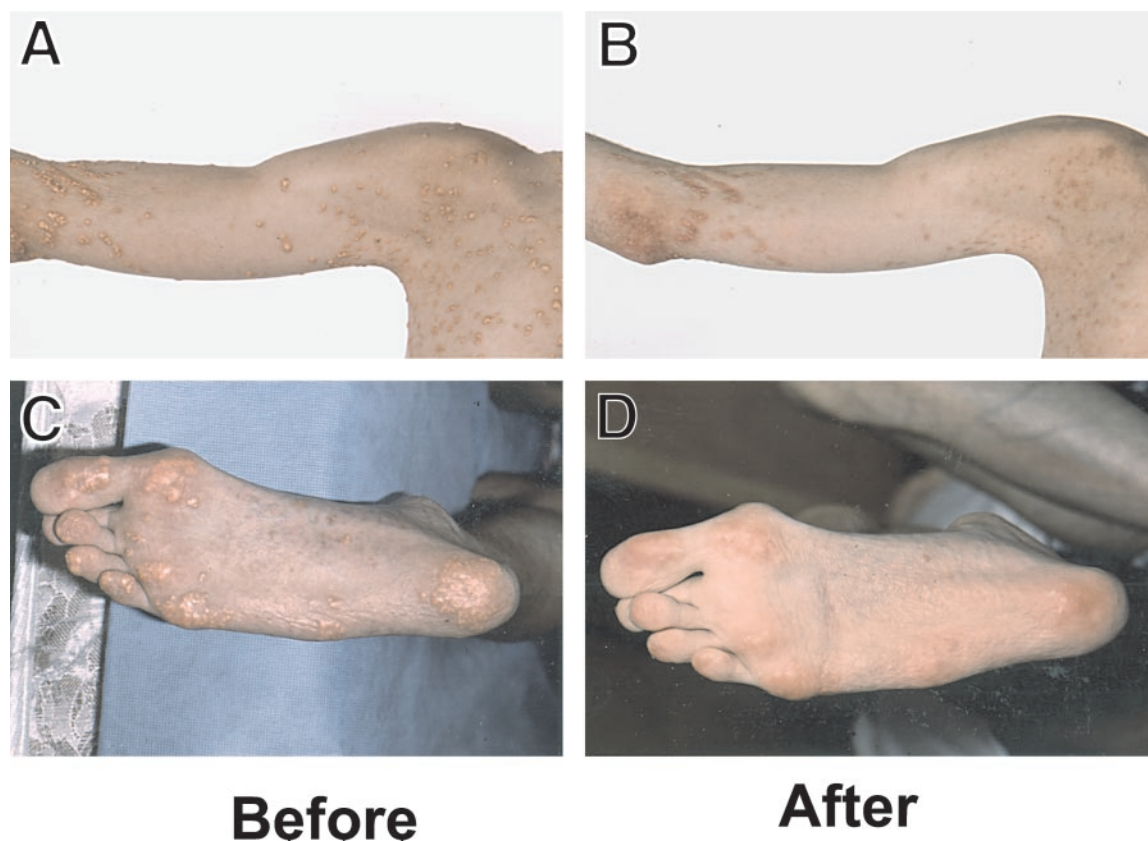


FIG. 3. Plasma exchange therapy was associated with marked regression of cutaneous xanthomata. Posterior scapular and plantar regions before (A and C) and after (B and D) therapy are shown.

trophic syndromes, management of dyslipidemia in these syndromes is often unsatisfactory using dietary approaches and available pharmacological agents. We have recently observed significant improvement in triglyceridemia with troglitazone therapy in a group of patients with lipodystrophy (4). However, troglitazone is contraindicated in patients with hepatic dysfunction, as in the current case. The magnitude of the elevation in lipid levels and the associated symptoms exhibited by this patient constitute the most severe presentation of generalized lipoatrophy seen in our center.

Our patient experienced rapid and dramatic clinical improvement in response to plasma exchange, with resolution of disfiguring facial xanthomas, marked diminution in the size of truncal and extremity xanthomas, and pronounced decrease in digital, palmar, and plantar pain due to a reduction in localized inflammatory reactions around eruptive xanthomata in these areas. A striking reduction in hepatic size was similarly documented in a subject whose hypertriglyceridemia had previously been refractory to dietary measures and therapy with multiple lipid-lowering medications. Clinical improvement began by the completion of the second procedure, with maximum benefit attained within 4 months of initiating therapy and sustained by continued weekly exchanges for the next 18 months. The patient was able to resume near-normal activities of daily living, including grooming and dressing herself without assistance, writing, playing the piano, and walking.

Plasma exchange was associated with a 60–85% acute

reduction in triglycerides and total cholesterol levels, with return to preapheresis values within 7 d. Consistent with these laboratory values, painful xanthomas began to reappear and/or regrow when the interval between consecutive procedures was greater than 7 d, prompting the patient to return and seek earlier treatment when apheresis was performed at longer intervals. During periods of dietary indiscretion or asthma exacerbation, triglyceride levels rebounded more quickly. Plasma exchange was thus useful as an adjunctive therapy to dietary control. Our data suggest that in the absence of reasonable adherence to a low fat diet, apheresis therapy would be less effective.

Blood lipid levels appeared to rebound more rapidly after larger (2.8-plasma volume) exchanges. This difference could not be quantitatively evaluated due to large variations in preapheresis lipid levels from procedure to procedure. It is possible that plasma factors that promote triglyceride clearance were depleted during plasma exchange; however, we found that apolipoprotein CII (a cofactor for lipoprotein lipase activity) did not decrease after the exchange. It is possible that other putative plasma factors promoting triglyceride clearance were depleted more profoundly during larger procedures. Lipid levels in our patient appeared to be most stable with weekly exchanges of 1.5–2.0 plasma volumes each.

Plasma exchange also had a favorable effect on the patient's insulin sensitivity, with a 30–40% decrease in fasting insulin and C peptide levels simultaneous with improved

glycemic control. Direct data from animal models as well as indirect data from humans suggest that lipid metabolism in the liver and muscle may be impaired in lipoatrophic states (2, 4). Acute lowering of lipid levels may thus have improved insulin sensitivity at the level of the liver and the muscle by decreasing tissue triglyceride levels.

This patient received more intensive plasma exchange therapy than any prior patient in our institution. Despite the frequency and volume of the exchanges, therapy was very well tolerated, with occasional mild vasovagal episodes responsive to volume infusion and no difficulties with peripheral venous access. The expected changes were noted in blood coagulation parameters and Ig levels (7) and did not result in either bleeding episodes or clinically relevant immune impairment. Plasma exchange is used as immunomodulatory therapy in immune-mediated neurological and hematological diseases, for which it is performed at less frequent intervals than reported in this study. However, neither the patient nor her primary physician noted an increased susceptibility to infection during treatment.

There was no charge to the patient or her insurance carrier for these procedures, because they were performed at a government research facility. However, the cost for a plasma exchange is typically about \$1500 in a hospital-based setting. Thus, the total cost for these procedures would have been about \$188,000. We recognize the potentially prohibitive nature of this cost, and that third party reimbursement would be complicated by the need to obtain prior approval for treatment of a nonstandard condition.

One prior study has reported the use of plasma exchange in a patient with acquired generalized lipoatrophy. Soler *et al.* (8) performed six exchanges during a 4-month period (two volume exchanges every 2–4 wk) as treatment for refractory pancreatitis. Pretreatment triglyceride elevations were less marked in their patient (2480 to 3011 mg/dl; 28 to 34 mmol/liter) and returned to baseline within 7–10 d before diminishing gradually during the course of treatment. The researchers believed that plasma exchange lowered lipid levels, but did not improve associated endocrine abnormalities, and was associated with cardiovascular complications (8). Other studies have used plasma exchange for short-term control of pancreatitis and other complications of hypertriglyceridemia associated with pregnancy, diabetes, or medications (9–13).

Our experience in this case indicates that intensive, long-term plasma exchange therapy may confer dramatic clinical benefit from the debilitating symptoms of severe hypertriglyceridemia and may safely be performed in patients whose symptoms are refractory to conventional drug and dietary therapy. Our findings are likely to apply not only to patients with the rare syndrome of acquired generalized lipoatrophy,

but also to those with other hyperlipidemic syndromes. Plasma exchange may produce striking benefits to quality of life until more definitive therapies become available.

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Address all correspondence and requests for reprints to: Elif Arioglu Oral, M.D., Diabetes Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Building 10, Room 8D20, 10 Center Drive, MSC 1770, Bethesda, Maryland 20892-1770. E-mail: elif\_arioglu@nih.gov.

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\* C.B. and E.A.O. contributed equally as primary investigators to this work.

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