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Relapsing and Progressive Complications of Severe Hypertriglyceridemia: Effective Long-Term Treatment with Double Filtration Plasmapheresis

Clemens Grupp[a, b] Johannes Beckermann[c] Eric Köster[d] Stephen Zewinger[e] Markus Knittel[f] Tilman Walek[g] Bernd Hohenstein[h] Beate Jaeger[i] Ralf Spitthöver[j] Reinhard Klingel[k, l] Cordula M. Fassbender[k] Bartosz Tyczynski[m]

[a]Department of Nephrology, Academic Teaching Hospital Bamberg, Bamberg, Germany; [b]Department of Nephrology and Rheumatology, Georg-August University Goettingen, Göttingen, Germany; [c]Department of Nephrology, St. Marien Hospital Vechta GmbH, Vechta, Germany; [d]Department of Internal Medicine II, Hospital of Barmherzige Brüder, Trier, Germany; [e]Department of Internal Medicine IV-Nephrology, Saarland University Hospital, Homburg, Germany; [f]Joint Practice of Internal Medicine, Witten, Germany; [g]Kiel Kidney and Vascular Center, Kiel, Germany; [h]Nephrological Center, Villingen-Schwennigen, Germany; [i]Dialysis and Lipid Center North Rhine, Mülheim an der Ruhr, Germany; [j]Dialysis and Lipid Center North Rhine, Essen, Germany; [k]Apheresis Research Institute, Cologne, Germany; [l]First Department of Internal Medicine, University of Mainz, Mainz, Germany; [m]Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Keywords
Double filtration plasmapheresis · Hypertriglyceridemia · Acute pancreatitis · Atherosclerotic cardiovascular disease · Lipodystrophy · Pregnancy

Abstract
Background: Severe hypertriglyceridemia (HTG) is associated with major complications such as acute or relapsing pancreatitis (AP) and atherosclerotic cardiovascular disease (ASCVD). Rapid elimination of triglyceride (TG)-rich lipoproteins (LP) with double filtration plasmapheresis (DFPP) without need for substitution has been found to be effective for the acute, short-term treatment of HTG-induced AP. Data on the long-term use of DFPP to prevent HTG-associated complications are scarce. ***Objectives:*** To evaluate the use and efficacy of regular DFPP treatment in clinical practice for preventing recurrence of HTG-associated complications in therapy refractory patients. ***Methods:*** Retrospective multicenter study in patients with severe symptomatic drug and diet refractory HTG with regular DFPP treatment. Patients' incidence of HTG-associated pancreatic or cardiovascular complications was compared before treatment and with regular DFPP treatment. ***Results:*** Ten patients (3 female) were identified with baseline maximal TG concentrations of 2,587–28,090 mg/dL (median 5,487 mg/dL; interquartile range [IQR] 4,340–12,636). The mean observation period was 3.9 ± 3.4 years before and 3.8 ± 3.0 years after commencement of DFPP. In 5 patients, severe HTG was related to chylomicronemia, 2 patients had familial partial lipodystrophy Dunnigan, and 1 patient had additional LP(a)-hyperlipoproteinemia. The main HTG-associated complication was recurrent AP in 8 patients, including 1 patient treated during pregnancy. Two patients presented severe progressive ASCVD. With long-term DFPP treatment, the annual rate of HTG-associated pancreatic or cardiovascular complications declined from median 1.4 (IQR 0.7–2.6) to 0 (IQR 0.0–0.4; $p < 0.005$). The absolute number of events was reduced by 77%. In 6 patients (60%) episodes of AP did not occur, nor was progression of ASCVD detected clinically or by routine imag-

karger@karger.com
www.karger.com/bpu

Dr. Cordula M. Fassbender
Apheresis Research Institute
Stadtwaldgürtel 77
DE–50935 Cologne (Germany)
E-Mail fassbender@apheresis-research.org

ing techniques. DFPP was effective in the elimination of TG-rich LP from plasma, and was safe and well-tolerated. ***Conclusion:*** Long-term, regular DFPP treatment resulted in stabilization of patients with severe HTG and related recurrent AP or progression of ASCVD, who were refractory to conventional dietary and drug therapy.

Introduction

The complex causes of hypertriglyceridemia (HTG), which are associated with a highly variable clinical appearance, make diagnosis and therapy an interdisciplinary challenge. Increased synthesis or defective clearance can lead to an increase of triglyceride (TG)-rich lipoproteins (LP) in plasma. According to a recently simplified classification, HTG is defined as either mild-to-moderate, with a plasma TG concentration of 2–10 mmol/L (175–885 mg/dL) and a more likely polygenic or secondary basis, or, rarely, severe, with a TG concentration of >10 mmol/L, (>885 mg/dL), more likely related to monogenic causes affecting only 0.1% of adults [1, 2]. Severe HTG primarily results from genetic disorders leading to a decrease in LP lipase activity. Uncontrolled diabetes mellitus, drugs, nephrotic syndrome, obesity, and alcohol intake are secondary causes. Severe HTG is associated with serious complications such as acute pancreatitis (AP) with high risk of frequent relapse and atherosclerotic cardiovascular disease (ASCVD). Elevated TG-rich LP represent an independent causal risk factor for ASCVD [2, 3]. The results of a large Mendelian randomization study suggested that all apolipoprotein B (ApoB)-containing LP particles, including TG-rich very-low-density lipoprotein (VLDL) particles and their metabolic remnants, as well as low-density lipoprotein (LDL) particles, have approximately the same effect on the risk of cardiovascular disease per particle [4].

Severe HTG accounts for up to 10% of all AP cases in nonpregnant individuals and is the third most common cause of AP after gallstones and alcohol. AP requires urgent therapy to prevent pancreatic necrosis, which has a mortality rate of up to 30% [5]. In pregnancy, up to 50% of all AP cases are related to HTG [6]. In the context of risk for HTG-induced AP, (HTG-AP) the threshold of TG levels >1,000 mg/dL is mentioned most frequently, which should be regarded as equivalent to severe HTG [5].

Standard treatment of HTG consists of dietary restrictions and lipid-lowering medication, such as fibrates and omega-3 fatty acids. In medical emergencies, effective and rapid lowering of excessively elevated TG with therapeutic apheresis to control HTG-AP is recommended by national and international apheresis guidelines [7, 8]. In general, 1–3 daily treatments of plasma exchange or double filtration plasmapheresis (DFPP) are performed. DFPP is a selective method of LP apheresis based on membrane plasma separation with subsequent plasma filtration of high-molecular-weight LP from plasma. Clinical data on the long-term use of therapeutic apheresis to prevent recurrence of HTG-associated complications are scarce and limited to plasma exchange [9–13]. For this indication, a selective procedure, such as DFPP, might be preferred to avoid the need for substituting human plasma products with their potential adverse effects.

The aim of our nationwide retrospective study was to assess the clinical practice and to evaluate the efficacy of long-term DFPP for patients with severe symptomatic HTG. For the first time, a larger case series with regular DFPP treatment for this rare indication was analyzed, including 2 patients with familial partial lipodystrophy (FPLD) who are, to our knowledge, the first cases described in the literature.

Methods

Patents and Outcome Measures

An open, retrospective, multicenter, noninterventional study throughout Germany was performed. Data collection period was between March 2018 and March 2019. Criteria for patient enrollment were diagnosis of severe HTG; insufficient response to appropriate diet and lipid-lowering drug therapy, including antidiabetic drugs, which were associated with relapsing or progressive HTG-related pancreatic or cardiovascular complications; and regular treatment with DFPP. The protocol was approved by the Ethics Committee of Bayerische Landesärztekammer (No. 17090) and the Ethics Committee of University Duisburg Essen (No. 18-8500-BO) and was reported to an open source online registry (No. DRKS00011704). The trial was performed in accordance with the principles of the Declaration of Helsinki. All patients provided written, informed consent before enrollment. The clinical course before and with regular DFPP was recorded. Individual retrospective observation periods were determined by the date of commencing regular DFPP treatment and the date of data collection for the study. The analyzed time before DFPP treatment varied depending on available clinical data of the individual patient.

The main outcome parameter for efficacy was the incidence of HTG-associated pancreatic or cardiovascular complications before and after commencement of DFPP treatment. HTG-associated complications were defined as follows: event of AP, episode of severe abdominal pain in patients with history of recurrent AP, and event or progression of ASCVD as determined clinically or by routine imaging technique. An ASCVD event was accounted by occurrence of cardiovascular death, nonfatal myocardial infarction, coronary bypass surgery, percutaneous coronary intervention, or stent. Progression of ASCVD without clinical event was accounted as an equivalent event with the following findings by routine imaging techniques: incidence of new or additional ASCVD at a new vascu-

lar location or region, or deterioration of existing ASCVD. Secondary endpoints were evaluations of safety and tolerability using treatment protocols in patient records. The validity of clinical findings was ascertained with careful review of medical records and based on standardized case report forms with source data verification.

DFPP treatments were performed using a membrane plasma separator (Plasmaflo OP-08W) in combination with a plasma component filter (Cascadeflo EC-50W or Rheofilter ER-4000, all Asahi Kasei Medical, Tokyo, Japan) and the tubing system MF-430 or CMF-430 (Effe Emme, Cigliano, Italy) together with the Octo Nova Technology, SW version 4.30.5 (DIAMED, Cologne, Germany). In 2 patients with extreme chylomicronemia, plasma separation was switched from membrane to centrifuge technique using the Spectra Optia (Terumo BCT Inc., Lakewood, CO, USA) in combination with a plasma filter (Rheofilter ER-4000). For vascular access in 2 patients, peripheral veins were used. In 8 patients, arteriovenous fistulas were created for chronic treatment. The filtered plasma volume per treatment was 2,000–5,000 mL, representing in mean 113% (±31) of patients' plasma volume. Anticoagulation was performed with unfractionated heparin (in 2 patients combined with citrate).

Statistics

The *t* test for paired samples was used to analyze changes in annual event rates; $p < 0.01$ was considered significant. Descriptive statistics were provided as mean with SD or median with interquartile range (IQR).

Results

Characteristics of Patients

Ten patients were identified (3 female) with a median age of 43 years (IQR 35–48) at commencement of DFPP treatment. Patient characteristics are summarized in Table 1. Ten treatment sites were involved in extracorporeal treatment of the patients. The patients presented different forms of severe symptomatic HTG. In 5 patients (2–5, 7), HTG was associated with chylomicronemia. In 2 patients, the diagnosis of familial chylomicronemia syndrome (FCS) was considered very likely. In patient 2, a heterozygous mutation of the glycosylphosphatidylinositol-anchored high-density-lipoprotein-binding protein 1 (GPIHBP1) gene was detected. In patient 3, genetic testing was not available, but FCS scoring according to Moulin et al. [14] was 10, suggesting FCS. However, multifactorial CS was not completely excluded. Two patients had FPLD Dunnigan (8, 9), confirmed by genetic testing. Patient 10, in addition to severe HTG, had LP(a)-hyperlipoproteinemia (Lp[a]-HLP), possibly representing a phenotype of familial combined hyperlipidemia. Diabetes mellitus has to be addressed as a major condition aggravating treatment of HTG in 7 of the analyzed patients. In 4 patients, type 2 diabetes was regarded as an underlying disease. In 3 patients, diabetes mellitus was pancreoprive due to HTG-related pancreatitis episodes (1, 2, 6) or additional pancreas tumor surgery (6). Recurrent AP was the main HTG-associated complication in 8 patients (1–8), 1 woman (7) was treated during pregnancy. Two patients (9, 10) had a severe progressive ASCVD. Patient 10 had, in addition, episodes of pancreatitis.

Appropriate diet and lipid-lowering therapy, including antidiabetic drugs, were insufficient to prevent progression or recurrence of HTG complications. In particular, patients 9 and 10 received statins to reduce ASCVD risk. However, attainment of the LDL-C target for established ASCVD, which was reduced from 70 to 55 mg/dL according to the 2019 guidelines of the European Society for Cardiology, could not be evaluated as LDL-C measurement must be regarded as invalid with TG levels of 800 mg/dL and above [15, 16]. Due to unsatisfactory control of TG levels, therapeutic apheresis was indicated, and DFPP was chosen as selective modality. At the time of the current assessment in 2019, all but 1 patient (7) were on regular treatment.

DFPP Treatment

All patients received DFPP treatments – generally 1–2, with a maximum of 3 treatments per week at the discretion of the treating physician. One patient (7) was treated with DFPP only during pregnancy for 2 months within the third trimester. The range of baseline TG concentrations was 2,587–28,090 mg/dL (median 5,487 mg/dL; IQR 4,340–12,636). TG concentrations before/after DFPP treatment had means 2,865 mg/dL (±1,425) and 1,695 mg/dL (±1,375), respectively. In 2 patients (2, 8) with severe chylomicronemia, plasma separation using a membrane technique was impaired by accumulation of chylomicrons. Elimination of these very large TG-rich LP was improved by using a centrifuge technique for plasma separation in combination with a plasma filter. The individual mean reduction rate of TG varied from 17 to 83% (for details see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000506506). Regular DFPP was well-tolerated by all patients after analysis of 1,085 treatment sessions. Eight patients had an arteriovenous fistula for vascular access. Recurrent fistula thrombosis occurred in 1 patient (1) and could be resolved by thrombectomy and surgical revision. Minor adverse events typically associated with therapeutic apheresis methods (e.g., transient hypotension, dizziness, hematoma at vascular access, or nausea) were not reported in detail.

Clinical Course

Patients' clinical courses regarding HTG-associated complications before and with regular DFPP are depicted in Figure 1 (for additional details of cases see online sup-

Table 1. Baseline characteristics

Patient number	Age at start of DFPP	Gender	Body weight, kg	BMI, kg/m^2	TG baseline maximal, mg/dL	Total cholesterol baseline, mg/dL	Lp(a) baseline	Characteristics of dyslipidemia	Main HTG-associated complications	Family history for dyslipidemia	Diabetes mellitus	Lipid-lowering drugs
1	28	Male	125	36	6,127	562	<60 mg/dL	sHTG	AP	Positive	Yes, pancreoprive	Omega-3 fatty acids, fibrates, statins; ezetemib; nicotinic acid intolerance
2	43	Male	98	31	21,596	758	52 mg/dL	sHTG; CM, very likely FCS*[1]	AP	Negative	Yes, pancreoprive	Omega-3 fatty acids, statins, ezetemib; nicotinic acid and fibrates intolerance
3	42	Male	122	42	28,090	626	<0.3 mg/dL	sHTG, CM, very likely FCS*[2]	AP	Negative	Yes, type 2	Omega-3 fatty acids, statins; fibrates
4	44	Male	81	26	4,320	590	n.d.	sHTG, CM	AP	Positive	No	Omega-3 fatty acids; fibrates
5	34	Male	99	29.6	3,562	414	<5 mg/dL	sHTG, CM	AP	Negative	No	Omega-3 fatty acids, fibrates
6	50	Male	n.d.	n.d.	5,940	382	<7 nmol/L	sHTG	AP	Negative	Yes, pancreoprive	Omega-3 fatty acids, fibrates; ezetemib; nicotinic acids and statins intolerance
7	29	Female	48	18	9,000	164	n.d.	sHTG, CM	AP	Positive	No	Omega-3 fatty acids, fibrates; lipid lowering medication stopped during pregnancy
8	37	Female	80	28	14,805	469	2 mg/dL	sHTG, FPLD	AP	Positive	Yes, type 2	Fibrates, statins; omega-3 fatty acids; metreleptin ineffective
9	56	Female	85	27	2,587	304	11 mg/dL	sHTG, FPLD	ASCVD (CHD)	Positive	Yes, type 2	Statins, ezetrol, omega-3 fatty acids
10	49	Male	80	29	4,400	473	89 mg/dL	sHTG; Lp(a)-HLP	ASCVD (CHD; PAOD); + AP	Positive	Yes, type 2	Fibrates, ezetrol, statins

* FCS scoring 10 according to Moulin et al. [14].
[1] Heterozygous mutation GPIHPB1.
[2] Eruptive xanthoma and blood sample with typical creamy chylomicron layer.
DFPP, double filtration plasmapheresis; TG, triglyceride; AP, acute pancreatitis; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CM, chylomicronemia; FCS, familial chylomicronemia syndrome; FPLD, familial partial lipodystrophy; Lp(a)-HLP, lipoprotein(a)-hyperlipoproteinemia; PAOD, peripheral arterial occlusive disease; sHTG, severe hypertriglyceridemia; BMI, body mass index.

pl.). Clinical course during DFPP treatment was analyzed from the time of commencing DFPP until the time of data collection for each patient. The analyzed time before DFPP treatment varied depending on available clinical data of the individual patient. The mean retrospective observation period was 3.9 years (±3.4) before and 3.8 years (±3.0) after commencement of DFPP. With long-term DFPP treatment, the annual rate of HTG-associated pancreatic or cardiovascular complications declined significantly from median 1.4 (IQR 0.7–2.6) to 0 (IQR 0.0–0.4; $p < 0.005$; Fig. 2a). Additional subgroup analyses are provided in online supplementary Figure 1a, b. In total, 464 months were analyzed before commencement of treatment and 457 months were analyzed after commencement of DFPP treatment. Evaluated absolute numbers of HTG-associated complications were 44 before and 10 after commencement of DFPP in 10 patients (Fig. 2b). During regular DFPP treatment, the absolute number of

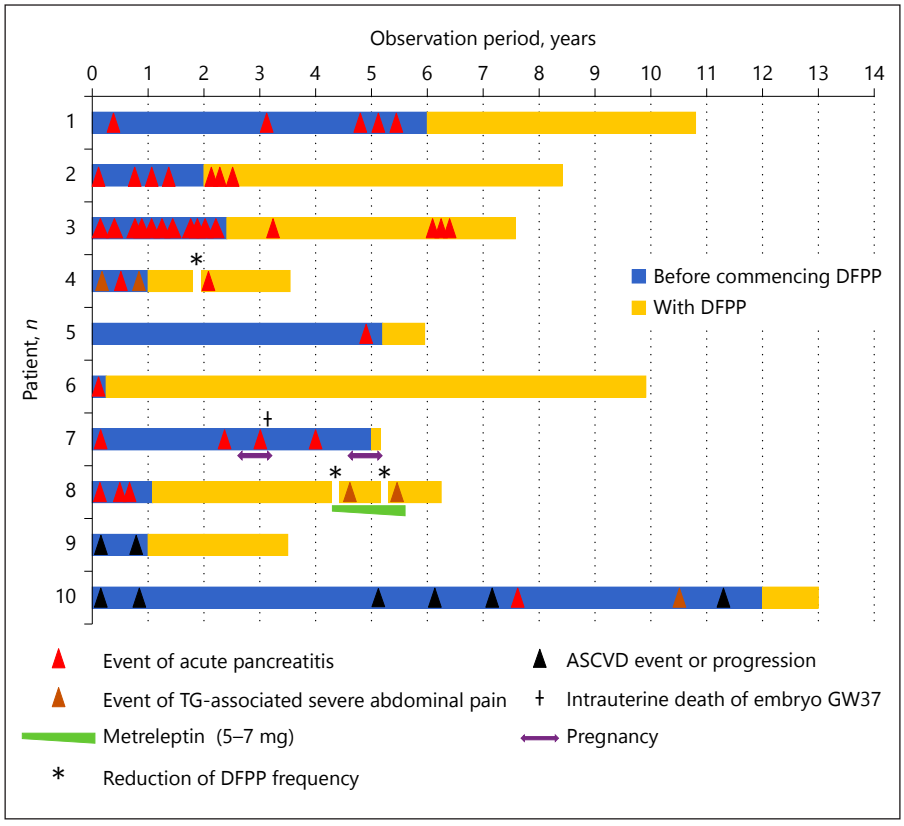

Fig. 1. Patients' clinical courses regarding HTG-associated events. Clinical course during DFPP treatment was retrospectively analyzed from the time of commencing DFPP until the time of data collection for each patient. The analyzed time period before DFPP treatment varied depending on available clinical data of the individual patient. Triangles represent events of AP (red), TG-associated severe abdominal pain (orange), and ASCVD event or progression (black) as detected by routine imaging techniques. Patient 4 missed single DFPP treatments due to temporary nonadherence to apheresis treatment. In Patient 8, DFPP treatment frequency was reduced during therapy trial with metreleptin. Patient 7 was treated with DFPP during the last trimester of her second pregnancy. GW, gestation week; TG, triglyceride; DFPP, double filtration plasmapheresis; ASCVD, atherosclerotic cardiovascular disease.

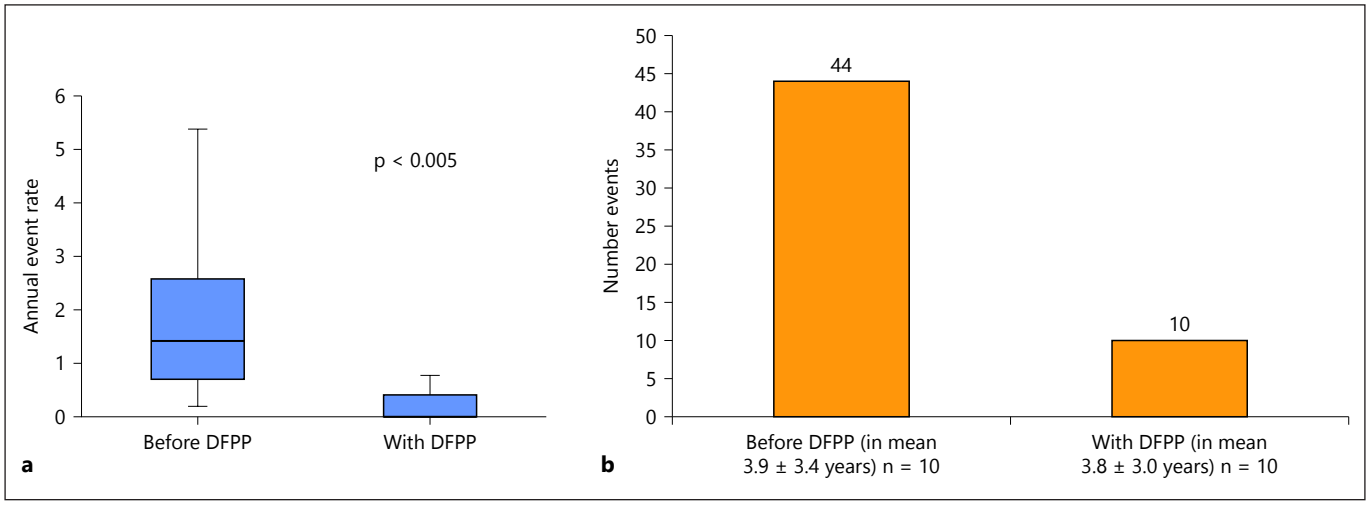

Fig. 2. a Annual rate of HTG-associated events including the composite of pancreatic and cardiovascular complications in patients with severe HTG (n = 10). The mean retrospective observation period was 3.9 years (±3.4) before and 3.8 years (±3.0) after commencement of DFPP. Decrease of annual event rate from median 1.4 (IQR 0.7–2.6) before to 0 (IQR 0.0–0.4) after commencement of DFPP treatment (t test for paired samples $p < 0.005$, n = 10). **b** Absolute numbers of events before and after commencement of DFPP treatment in patients with severe HTG (n = 10). In total, 464 months were analyzed before commencement and 457 months after commencement of DFPP treatment. HTG-associated events were defined as follows: event of AP, episode of severe abdominal pain in patients with history of recurrent AP, or event or progression of ASCVD as determined clinically or by routine imaging technique. DFPP, double filtration plasmapheresis.

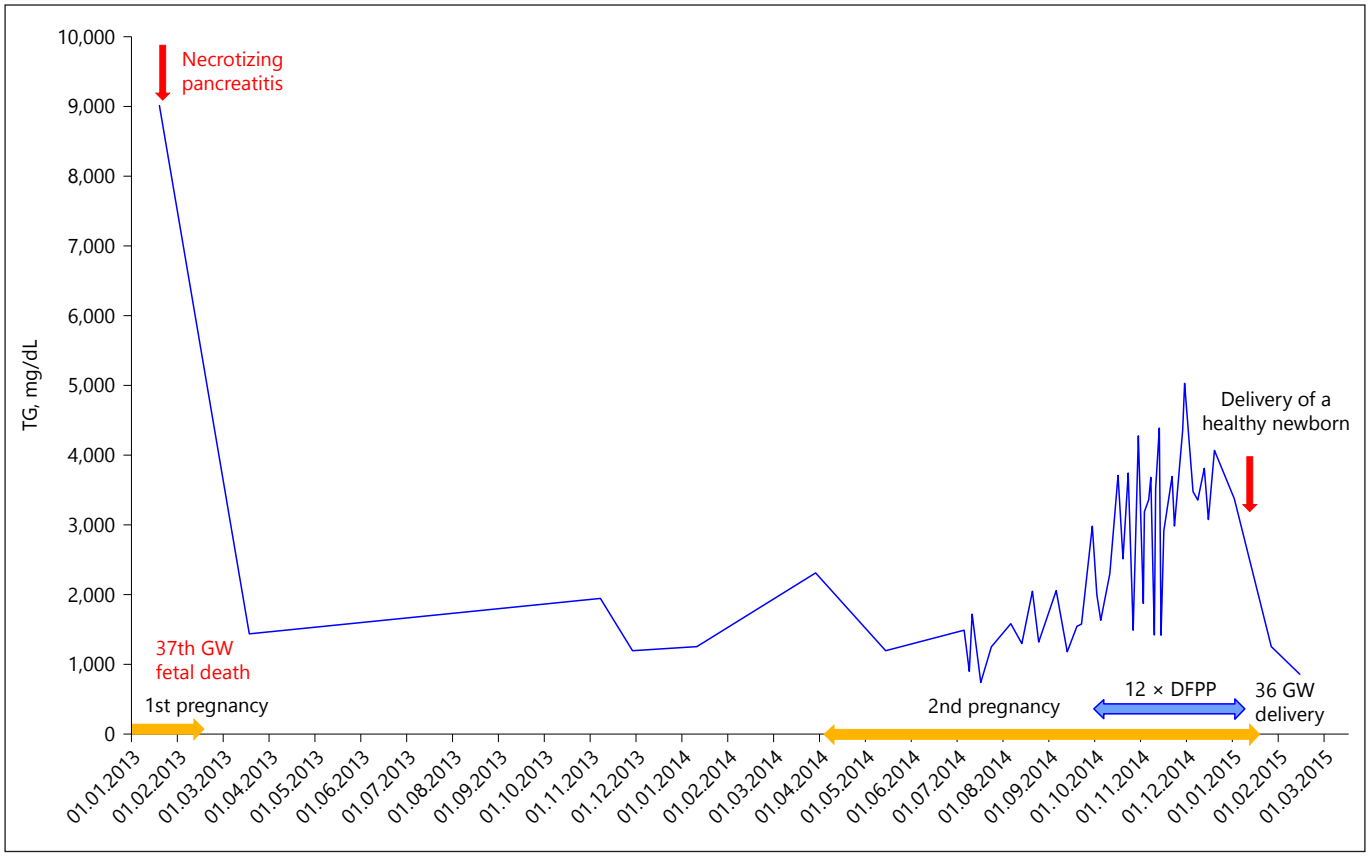

Fig. 3. DFPP treatment during pregnancy. TG levels and clinical course of patient 7. GW, gestation week; TG, triglyceride; DFPP, double filtration plasmapheresis.

events declined by 77%. In 6 cases (60%), including the pregnant patient, episodes of AP did not occur, nor was progression of ASCVD detected clinically or by routine imaging techniques. TG values during the pregnancy and clinical course of patient 7 are depicted in Figure 3.

Discussion

The role of long-term DFPP as final treatment escalation for relapsing or progressive complications of severe HTG was analyzed in 10 patients. HTG in these patients had different etiologies and different pathogenic profiles. Diabetes mellitus was a comorbid condition of severe HTG in 7 patients. In 4 of these patients, diabetes mellitus existed as an underlying disease. In 3 patients, it developed due to deterioration of pancreas function (pancreoprive). Chylomicronemia was present in 5 patients. Two patients had the very rare form of FPLD Dunnigan. The indication for regular DFPP treatment to prevent HTG-associated complications (i.e., recurrent HTG-AP) or progression of ASCVD was established during routine care. The general approach for the long-term treatment of HTG, aiming at preventing HTG-associated complications like HTG-AP, includes dietary counseling, fat restriction, medium chain TGs, weight loss, avoiding alcohol intake, strict glycemic control in diabetes, and lipid-lowering drugs [17]. However, standard treatment strategies may be insufficient to prevent complications in some patients with severe HTG due to very rare monogenic forms or individual comorbid conditions or predisposing factors.

HTG-AP

Recurrent HTG-AP was the main complication in 80% of patients in this study. HTG-AP is a rare and complex disorder with an underlying mechanism that is influenced by genetic, metabolic, environmental, and patient-specific factors [17]. In guidelines for the treatment of acute or chronic pancreatitis prevention of HTG-AP, relapse is not receiving appropriate attention. It has been

recognized in current guidelines on the use of therapeutic apheresis [8]. Clinical studies are sparse. Plasma exchange and DFPP have also been found to be safe and effective for the emergency treatment of severe HTG-AP during pregnancy [6, 18–28]. Shortening of hospitalization was reported as a major benefit [23, 29]. The pathogenic model of HTG-AP includes disturbance of pancreatic microcirculation by very large TG-rich LP. The accumulation of chylomicrons reduces pancreatic capillary flow with resulting ischemia. Subsequent hydrolytic release of free fatty acids is toxic to the pancreatic endothelium and acinar cells. Activation and release of pancreatic enzymes induces autodigestion-related injury [5]. The rationale for the use of therapeutic apheresis is rapid extracorporeal elimination of TG-rich LP, which is hypothesized to instantly stop further organ damage. DFPP treatment results in the improvement of blood flow and microcirculation [30]. It is generally believed that TG levels >1,000 mg/dL trigger AP and its serious complications. However, this threshold for the risk of HTG-AP appears rather arbitrary [23, 31]. Not all patients with severe HTG develop AP, and many patients with severe HTG never develop AP. In a recent retrospective study evaluating patients with very severe HTG and TG >2,000 mg/dL, in 62%, no episodes of AP were reported [32]. Also, the correlation of pancreatitis severity and TG level is different in individual patients [19]. In one study more severe forms of pancreatitis were observed in patients with higher TG levels compared to a group with lower TG levels, suggesting that high TG level may be associated with poor prognosis [33]. In our study, clinical stabilization of patients was observed even though the TG concentration in plasma was not reduced to a mean level of <1,000 mg/dL in all patients, suggesting that additional individual predispositions for AP might be decisive. It can be hypothesized that the therapeutic effect of regular DFPP treatment is based on the pulsed immediate physical extracorporeal elimination of large LP with their load of oxidized lipid components from plasma, thus subsequently reducing other pathophysiological processes of pancreatitis and atherosclerosis such as inflammation, oxidative stress, and impaired rheology [30, 34, 35]. With long-term DFFP, the incidence of AP was reduced in all affected patients in this study compared to the evaluated time period before commencing DFPP. A reduction of DFPP treatment frequency was followed by AP relapse and typical symptoms of TG-associated abdominal pain, respectively, in 2 cases (4, 8). These results indicate a preventive effect of DFPP treatment.

Familial or Multifactorial Chylomicronemia Syndromes

TG concentrations of >2,000 mg/dL are indicative of large quantities of chylomicrons, which are composed of 86% TG. In the rare form of FCS arising from a genetic defect in intravascular lipolysis, such as LP lipase or GPIHBP1, differentiation of FCS from MCS is difficult since the clinical and biochemical phenotype can be very similar, whereas the incidence of HTG-AP is more frequent in FCS. Methods of genetic assessment are not always available. Recently, a pragmatic diagnostic scoring system for FSC was suggested [14]. The scoring system revealed the diagnosis of FCS as very likely for 2 patients in our cohort (2, 3) with histories of multiple AP. In 2, a heterozygous mutation in GPIHBP1 was detected by gene analysis. Patient 3 presented eruptive xanthomas and chylomicrons were visible as the typical creamy layer on full blood samples. With long-term DFFP treatment, the frequency of HTG-associated complications was markedly reduced in both patients. Antisense-mediated inhibition of hepatic APOC3 mRNA with volanesorsen represents a novel pharmacological option to lower TG levels for the very rare patients with confirmed monogenic FCS and failure of a strict low-fat diet, which has been investigated in phase 3 clinical trials, but long-term experience in routine care is not available [36]. Thrombocytopenia and injection-site reactions were reported as common adverse events [36]. Thrombocytopenia is no relevant side effect of DFPP [37]. The annual treatment cost for volanesorsen in Germany in 2019 was >600,000 Euro which is approximately 10 times that of DFPP.

HTG-AP during Pregnancy

In pregnancy, hormonal changes and a decrease in LP lipase activity predispose one to increased TG levels, mostly in the third trimester. TG-lowering drugs are contraindicated. In particular, in women with an existing dyslipidemia, pregnancy may cause severe HTG with a high risk of HTG-AP [17]. As in general, individual susceptibility differs – some pregnant women may tolerate higher TG levels without significant symptoms. AP is associated with life-threatening fetal complications and increased maternal mortality [23]. Our patient (7) with a known history of severe HTG and recurrent AP experienced intrauterine fetal death during her first pregnancy. Therapeutic apheresis was not considered at this time. With regular DFPP treatment during the third trimester, the second pregnancy continued without complications until the timely delivery of a healthy newborn. The pro-

phylactic use of therapeutic apheresis to avoid HTG-AP in individual high-risk women during pregnancy seems to be rare in clinical practice – there are only a few case reports, including one describing effective treatment with DFPP [6, 38, 39]. Interdisciplinary cooperation of gynecologists, lipidologists, and nephrologists caring for women with previously known severe symptomatic HTG during pregnancy should become mandatory in these rare cases.

Combination of HTG- and Lp(a)-HLP

One patient (10) presented combined TG- and Lp(a)-HLP associated with severe progressive ASCVD involving coronary and peripheral arteries despite conventional dietary and drug therapy, including effective lowering of LDL-C. Elevated ApoB-containing TG-rich LP are an independent causal risk factor for ASCVD. High concentration of TG is strongly associated with increased risk for myocardial infarction, ischemic stroke, and early death [1, 2, 40]. The atherogenic potential of elevated TG is underdiagnosed and undertreated due to diagnostic difficulties and rare occurrence. Most forms of HTG are combined with other dyslipidemias. The atherogenicity of TG is not only dependent on the concentration of TG but also on the composition of the TG-rich LP particles in the blood and their influence on lipid metabolism. With Mendelian randomization analyses, a similar risk reduction of ASCVD was found in TG-lowering LP variants and LDL-C-lowering LDL-receptor variants [4]. However, there is not yet conclusive evidence on whether lowering TG reduces the risk of ASCVD. Lp(a) is an independent causal cardiovascular risk factor, enhancing the risk of premature or progressive ASCVD. Regular LP apheresis can prevent cardiovascular events in patients with progressive ASCVD and Lp(a)-HLP [35]. Lp(a)-HLP, along with progressive ASCVD, is approved as an indication for regular LP apheresis in Germany. For patient 10 with a combination of HTG- and Lp(a)-HLP (TG >3,500 mg/dL; Lp[a] >80 mg/dL), regular DFPP treatment was of particular benefit as Lp(a) was eliminated with the same efficacy as LDL-C, and even greater efficacy than TG. With regular DFPP, progression of ASCVD could be prevented.

HTG and Lipodystrophy Syndromes

Lipodystrophy (LD) syndromes are extremely rare disorders of deficient leptin action and body fat homeostasis associated with serious metabolic complications, including diabetes, HTG, and steatohepatitis [41]. Dietary approaches and available pharmacological agents are often unsatisfactory in LD. Lipodystrophies are categorized in congenital generalized LD, FPLD and acquired generalized or partial LD. Diagnosis of LD is generally based on medical history, physical examination, body composition, and metabolic status [41]. LD is a serious and complication-prone disease. Data on the use of therapeutic apheresis as an ultima ratio option to reduce TG are scarce. Intensive, long-term plasma exchange therapy with dramatic clinical benefit has been described in 1 girl with acquired, generalized LD [42]. Two patients of our cohort were diagnosed with FPLD-type Dunnigan, with main complications of AP in 8 and ASCVD in 9. The majority of FPLD are autosomal dominant [43]. Phenotypically, patients with FPLD lack extremity and gluteal subcutaneous fat, which becomes obvious around puberty in most cases. FPLD2, also known as the Dunnigan variety of FPLD, is caused by autosomal dominant mutations in the *LMNA* gene on chromosome 1q21-22 [43]. *LMNA* encodes nuclear lamin A/C. Cardiovascular complications include CHD and hypertension, while metabolic complications include insulin resistance, diabetes mellitus, HTG with resultant pancreatitis, and hepatic steatosis, which tend to increase with age. Women can also have preeclampsia and miscarriages. Many complications of FPLD are secondary to deficient adipose tissue, like insulin resistance, leading to severe HTG and AP. Treatment with recombinant human methionyl leptin (metreleptin) may be considered for patients with FPLD and severe metabolic derangements (hemoglobin A1c >8%, and/or TG >500 mg/dL). In 8, who was clinically stable with regular DFPP, metreleptin treatment was not effective. Reduction of DFPP frequency during metreleptin treatment led to increased TG concentrations even above 6,000 mg/dL. Simultaneously, the patient developed typical symptoms of TG-associated abdominal pain. Our results correspond to the findings that in FPLD, the response to metreleptin is less robust than in generalized LD [41]. There is evidence of an increased risk of early ASCVD in subjects with FPLD and *LMNA* mutations, notably in women [41, 44]. Both female patients in our study with known mutations in the LMNA gene coding for Lamin A/C presented 2-vessel coronary artery disease; patient 9 exhibited a very progressive course. After commencing regular DFPP treatment, no progression of ASCVD was observed in either case.

Therapeutic Apheresis – Methodological Aspects

Data on the long-term use of therapeutic apheresis to prevent relapse or progression of HTG-associated complications are mostly limited to plasma exchange [9–13].

A selective method of LP apheresis capable of eliminating large TG-rich LP, like DFPP, might be preferred to avoid the regular need for substituting human plasma products. Protein replacement fluids bear the risk of allergic reactions, as well as a small but clinically relevant risk of virus transmission [45, 46]. With long-term DFFP treatment, the frequency of HTG-associated complications was reduced by 77% in our cohort compared to the analyzed time period before commencing DFPP. No relevant side effects were reported during DFPP. Sides effects related to vascular access are not specifically attributable to DFPP.

In rare cases with extremely large quantities of chylomicrons with a particle size of 75–1,200 nm, membrane plasma separation can be impaired. Treatment in a fasting state can be favorable to minimize the negative impact of postprandial increase of chylomicrons, remnants, or large VLDL on the filtration process. The use of centrifugal plasma separation combined with plasma filtration represents a methodological alternative; however, the availability is mostly limited to in-hospital treatments. In 2 patients (2, 8) of this case, series reduction of very large TG-rich LP was improved with a change to this method. In-hospital care of acute HTG-associated complications is regulated in Germany. DFPP and PE are implemented with equal cost in the coding system for hospital reimbursement. In 2019 reimbursement was 1,278 Euro per treatment.

However, for long-term outpatient DFPP treatment of high risk patients with severe HTG, an individual approval for reimbursement by the statutory or private health insurance fund is necessary, representing a substantial hurdle for actual clinical use.

Limitations

The retrospective nature of the analysis, variable observation periods, the relative small number of patients, and lack of a control group of patients are limitations of the presented study results. A potential confounding factor could be the intensive patient care by doctors and nurses during weekly treatments of the patients.

Conclusion

With long-term DFPP, the incidence rate of HTG-AP and progression of ASCVD was substantially reduced in select, high-risk patients with severe HTG which had failed to be eliminated by prior standard therapies. These results include rare genetic forms, such as FPLD, and particular comorbid or clinical conditions, such as pancreoprive diabetes mellitus or pregnancy. Based on the limited data, only patients who had already suffered severe complications can be candidates for secondary prevention by long-term apheresis treatment. A larger prospective trial would be required to ascertain conclusively the benefits of long-term DFPP as an escalating treatment for severe refractory forms of HTG. However, it might not be feasible to enroll a sufficient number of patients with such rare morbid conditions in a controlled study design, which also – from an ethical point of view – might be problematic in regard to the putative benefit of therapeutic apheresis in these rare, high-risk patients.

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None.

Statement of Ethics

Ethical approval for the study was obtained. All patients gave their written informed consent.

Disclosure Statement

C.G. received honoraria from Berlin Chemie, Berlin, Germany; Bristol-Myers Squibb, New York, USA; Hexal, Holzkirchen, Germany; Novartis, Basel, Switzerland. J.B. received honoraria from AMGEN, Munich; Sanofi, Frankfurt. R.S. received honoraria from AMGEN GmbH, München, Germany, Sanofi, Paris, France. C.M.F. and R.K. are employees of Apheresis Research Institute, which received research grants from Diamed, Cologne, Germany and Asahi Kasei Medical, Tokyo Japan. All other authors have no conflicts of interest to declare.

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Author Contributions

C.G., J.B., E.K., S.Z., M.K., T.W., B.H., B.J., R.S., and B.T. were clinical investigators and collected data. C.G., C.M.F., and R.K. contributed to the design and implementation of the research, to the analysis of the results, and the writing of the manuscript. All authors reviewed the final manuscript.

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