FDA Executive Summary

Prepared for the
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Pediatric Advisory Committee

H120005
Liposorber® LA-15 System

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review provides a safety update based on the postmarket experience with the use of the Liposorber® LA-15 System (hereafter referred to as Liposorber LA-15) from Kaneka in pediatric patients for the treatment of nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) since approval in 2013. The Liposorber LA-15 System, a blood processing system that is used outside the body, includes disposable components and a control/monitor unit. The device works by removing certain lipoproteins from the patient's blood. The patient's blood is first passed through a plasma filter where the blood cells are separated from plasma (the liquid component of the blood). The plasma is then further passed through two adsorption columns, which are packed with a gel designed to capture the lipoproteins in the blood. The blood cells and the treated plasma are then returned to the patient via the blood return line.

II. INDICATIONS FOR USE

The Liposorber® LA-15 System is indicated for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis, when

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated, and the patient has a GFR $\geq$ 60 ml/min/1.73m^2, or
- The patient is post-renal transplantation.

III. BRIEF DEVICE DESCRIPTION

The Kaneka Liposorber® LA-15 System is an integrated extracorporeal blood processing system that includes disposable components and a control/monitor unit.

The components of the device are identical in material and design to the device currently approved via PMA P910018 (for subgroups of patients with familial hypercholesterolemia (FH)) and its supplements. The Liposorber® LA-15 System consists of four major components: the Sulflux KP-05 Plasma Separator, Liposorber® LA-15 Adsorption Columns, NK-M3R Tubing Set, and MA-03 Machine.

While the Liposorber® LA-15 System (P910018) is labeled for either weekly or bi-weekly use when used to treat familial hypercholesterolemia (FH) (depending on the patient's LDL-C levels), in the Humanitarian Device Exemption (HDE), the Liposorber (H120005) is indicated for up to 12 uses in 3 months (twice weekly for 3 weeks then weekly for 6 weeks) for treatment of focal segmental glomerulosclerosis (FSGS).

IV. REGULATORY HISTORY

The Liposorber LA-15 System received designation as a Humanitarian Use Device (HUD) Designation on September 28, 2012, and on October 10, 2013, the HDE application was approved by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration.

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. Since each Liposorber LA-15 system treatment regmen includes 12 treatments/patient, the total ADN is 96,000.

Section 613(b) of the FDASIA states that an HDE holder of a HUD for which an HDE was approved prior to the enactment of FDASIA on July 9, 2012 may submit an HDE supplement (21 CFR 814.108) requesting an exemption from the profit prohibition for a HUD. On September 4, 2012, the firm requested a determination that the Liposorber® LA-15 System met the conditions of either subclause (I) or (II) under section 520(m)(6)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the FDASIA, so that the device might be sold for profit. The HDE supplement request was approved by the FDA on October 10, 2013.

As stated in section 520(m)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

Table 1 below provides the number of device components distributed by the firm for the calendar year 2020 in the United States

Table 1. Annual Distribution Number-Calendar Year Jan-Dec 2020

Device	Total Sales
MA-03 Apheresis Machine	0
Liposorber® LA-15 LDL Adsorption Column (2 columns/shipment)*	384
Sulflux® KP-05 Plasma Separator	384
NK-M3R (U) Tubing System for Plasmapheresis	354

*Each shipment of adsorption columns contains two columns. Therefore, 384 shipments would include 768 columns.

VI. POSTMARKET DATA: POST-APPROVAL STUDY (PAS)

a. PAS Conditions of Approval:

The Liposorber HDE (H120005) was approved on October 10, 2013

The purpose of the PAS study is to evaluate the long-term safety and probable benefit of the Liposorber LA-15 System for the treatment of pediatric patients who have FSGS with an estimated Glomerular Filtration Rate (eGFR) ≥60 ml/min/1.73 m^2 accompanied by nephrotic syndrome in which standard treatment options are unsuccessful or not well tolerated or for the treatment of pediatric post renal transplant patients with nephrotic syndrome associated with primary FSGS.

This is a prospective, multicenter, single arm study with a total of 35 newly enrolled patients, treated at 3 to 10 clinical centers in the United States. The study participants will be followed for 24 months after the completion of the final apheresis procedure. The study visits will be as follows: Pre-procedural exams and laboratory tests, approximately 9 weeks of study apheresis procedures, and then for 1-, 3-, 6-, 12- and 24-month follow-up office visits after the last apheresis treatment.

The primary objectives of this study are to confirm the safety and probable benefit of the Liposorber LA-15 System in relieving nephrotic syndrome, defined as urine protein: creatinine ratio (Up/c) > 2.0 (gram protein per gram creatinine) with a first morning void urine sample, associated with refractory pediatric primary FSGS at 1 month after the final apheresis treatment.

The primary probable benefit endpoint is the percent of patients who show complete or partial remission at 1 month after the final apheresis treatment. Complete remission is defined as Up/c < 0.2 (g/g) with a first morning void urine sample. Partial remission is defined as at least 50% reduction in Up/c compared to the value at screening or Up/c between 0.2 and 2.0 (g/g) with a first morning void urine sample. A sample size of 30 patients is required for this analysis.

The primary safety endpoint is the rate of device-related and procedure-related serious adverse events (SAEs) occurring during the treatment period and up to 1-month follow-up visit. The rate of SAEs and corresponding 95% CI will be provided.

The secondary objectives are to evaluate safety and probable benefit of the Liposorber LA- 15 System in relieving nephrotic syndrome associated with refractory pediatric primary FSGS at 3 months, 6 months, 12 months, and 24 months after the final apheresis treatment. The secondary safety and probable benefit endpoints include: nephrotic condition (complete remission, partial remission, and nephrotic state) including the percentage of patients who obtain complete and partial remission at 3, 6, 12, and 24 months; incidence of adverse events encountered during the period in which apheresis treatments are given; incidence of all adverse events and SAEs occurring within 3, 6, 12, and 24 months after the final apheresis treatment; and laboratory values, including estimated glomerular filtration rate (eGFR) at baseline, after the last treatment, and at 1, 3, 6, 12, and 24 months after the final apheresis treatment, including percent change from baseline and percentage of patients showing an increase or decrease in each value.

b. PAS Study Status:

PAS study data was available from two reports:

1. The seven year interim post-approval study report (H120005/R017), received at the FDA on October 7, 2020,
2. The seven year annual report (H120005/R018), received at the FDA on December 24, 2020.

The sponsor reported that Institutional Review Board (IRB) approval had been obtained for six clinical sites, and twenty-three subjects had been enrolled since study inception (Table 2). The study was anticipated to have enrolled 20 subjects by September 2017, and enrollment was anticipated to be completed in August 2018.

Table 2. PAS Study: Patient Enrollment and Study Status

Interim Report	Date Received	Sites Enrolled	Patients Enrolled	Study Status	Actions Taken by FDA
6-month (R001)	7/8/14	0	0	Study Pending	
12-month (R002)	10/2/14	0	0	Progress Adequate	
18-month (R004)	4/6/15	3	0	Progress Adequate	
24-month (R005)	10/1/15	3	4	Progress Adequate	
36-month (R007)	10/4/16	3	9	Progress Inadequate	• Worked with sponsor to revise study timeline • Provided recommendations for enrollment strategies
39-month (R008)	12/28/16	4	9	Progress Adequate	
48-month (R010)	10/13/17	6	14	Progress Inadequate	• Deficiency letter issued to request plan from sponsor for improving enrollment
60-month (R013)	10/09/18	7	14	Progress Inadequate	• A teleconference will be scheduled with the sponsor to identify current enrollment barriers and alternatives to improve it.
72 month (R015 and R016)	09/12/2019 and 12/25/2019	7	17	Progress Adequate	
84 month (R017 and R018)	10/07/2020 and 12/28/2020	7*	23	Progress Adequate	

Since the last report:

- One (1) new patient was enrolled in this study and reached 1-month follow-up (F/U)
- Three (3) other patients reached 6-month F/U
- Two (2) patients were withdrawn from the study
- One (1) patient moved to another location becoming unable for F/U
- One (1) patient needed to initiate additional series of apheresis treatment with the LIPOSORBER® LA-15 System (a major protocol deviation).

The distribution of subjects' demographics is presented in Table 3 below.
*One site (Weill Cornell Medicine/NewYork-Presbyterian, NY) withdrew from the study during the current reporting period

Table 3. Demographics of Enrolled Subjects (n=23)

	N	%
Age (years)		
6 - 8	7	30.4
9 - 11	6	35.3
12 - 14	6	35.3
15 - 17	1	0
18 - 20	3	13.0
Sex		
Male	12	52.2
Female	11	47.8
Race/ethnicity		
Caucasian	13	56.5
African American	6	17.4
Hispanic/Latino	2	8.7
Unknown	2	8.7

Source: Constructed based on data from H120005/R017

Follow-up is ongoing; its status per study visit is shown in Table 4 below. Of the 23 subjects enrolled in the study, there have been ten withdrawals before the final protocol visit, including two subjects in the current reporting period. The reasons for withdrawal are listed in Table 5 below. Four subjects are in active follow-up. Since study inception, there have been two protocol deviations (two patients who should have been excluded from study entry due to not meeting inclusion criteria). Those two subjects are still undergoing follow-up visits, as well as one subject who withdrew and then underwent a second round of treatment.

Table 4. Subject Follow-up per Study Visit

Study Visit	Completed	Withdrawn	Active
~9 weeks Apheresis Procedures	19[a, b]	0	0
1-month	14[b]	5	1
3-month	10[b]	3	0
6-month	9[b]	1	3
12-month	5[b]	1	0
24-month	4	0	0

[a] One subject did not start treatment due to thyroid disease; [b] Including two protocol deviations;
Source: Constructed based on data from H7120005/R013 and R015

Table 5. Reasons for Withdrawal/Exclusion

Subject/Patient ID	Status	Reason
1	Withdrew after 6M	Subject moved to another hospital and had further treatment off the study.
2	Withdrew after 3M	Subject relapsed and had another treatment series off the study.
3	Withdrew after final apheresis treatment	Subject dropped out and was lost to follow-up.
4	Exclusion (treatment not started)	Subject was revealed to have thyroid disease after enrollment (Medical Exclusion Criteria #8)
5	Withdrew after final apheresis treatment	Unknown
6	Withdrew after the final treatment	Moved to another location
7	Required second series of device treatments	Major protocol deviation
8	Exclusion (continuing active follow-up)	The reported eGFR level at baseline was 39.8 ml/min/1.73m^2, which fell out of the inclusion criteria of an eGFR > 60 ml/min/1.73m^2.
9	Withdrew after 12M	Unknown
10	Exclusion (continuing active follow-up)	The reported Up/c of ACH004 at baseline was 0.08, which indicated that the patient achieved complete remission before treatment and was considered be inappropriate for treatment.
11	Exclusion	Did NOT have a baseline urine P/C value recorded (required for inclusion)
12	Withdrew after 1M (continuing active follow-up after second round of treatment)	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment.

13	Withdrew after 1M (continuing active follow-up after second round of treatment)	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment.
14	Withdrew after 1M	Unknown
15	Withdrew after 1 M	Unknown

Source: Constructed based on data from H120005/R013, R015, and R017

Interim Results

Probable Benefit

Primary probable benefit endpoint: percentage of patients who show complete or partial remission at 1 month after the final apheresis treatment
Secondary probable benefit endpoint: percentage of patients who show complete or partial remission at 3, 6, 12, and 24 months after the final apheresis treatment

At one month follow-up, five of eleven (45%) subjects in whom Urine Protein/Creatinine Ratio (Up/c) data was available had achieved either partial (four subjects) or complete (one subject) remission. Two subjects (27%) had missing Up/c data at one month and therefore remission status was uncertain; both of these patients had nephrotic syndrome 3 months after the final Liposorber LA-15 treatment. Five of eight (63%) subjects who were followed for three or six months had complete or partial remission at the three or six month follow-up periods, while three of eight subjects (38%) had no remission (nephrotic syndrome, or NS, persisting). At 12-month follow-up, three of five (60%) subjects displayed either partial (1 subject) or complete (2 subjects) remission, while two of five (40%) subjects had persistent NS.

These outcomes and current status are shown in Table 6 below. Two subjects are not included in the table bacause they withdrew after the last treatment without follow-up labs or were ineligible for inclusion. Two subjects (baseline glomerular filtration rate 39.8 ml/min and urine protein-to-creatinine ratio not consistent with nephrotic syndrome) are not included in the table because they did not meet study inclusion criteria and therefore are considered protocol deviations and excluded from the probable benefit results; however these subjects continued follow-up visits. One subject met the criteria for nephrotic syndrome at 1, 3, 6, and 12-month follow-up. One subject met criteria for complete remission at 1, 3, 6, and 12-month follow-up.

Table 6. Remission Status Based on Urine Protein/Creatinine (Up/c) Ratio

Patient ID	1-month	3-month	6-month	12-month	24-month	Status
1	PR	PR	PR			Withdrew after 6 mo visit
2	N/A	NS				Withdrew after 3 mo visit
3	NS	PR	CR	CR	CR	Completed study

4	N/A	N/A	N/A	(-)	(-)	Active
5	PR	CR	PR	CR	CR	Completed study
6	NS	NS	NS	NS		Withdrew after 12 mo visit
7	NS					Withdrew after 1 mo visit
8	NS					Withdrew after 1 mo visit
9	PR	PR	PR	PR	PR	Active
10	NS	N/A	N/A	(-)	(-)	Active
11	N/A	NS	NS	NS	NS	Active
12	NS					Withdrawal
13	CR	CR	CR	(-)	(-)	Active
14	PR	(-)	(-)	(-)	(-)	Active

NS=Nephrotic Syndrome; PR=Partial Remisssion; CR=Complete Remission; N/A=Not available/Data Not Reported; (-)=Not Yet Followed-Up; [a] Gray shading indicates that data will not be collected (i.e., missing data or subject withdrew), and absence of shading indicates that data were or will be collected;
Source: Constructed based on data from H120005/R017

The Agency conducted an analysis of the outcomes of data for the fifteen (15) subjects who left the study early after completing all device treatments to ascertain if the exclusion of the data from those subjects may have skewed the results. Below are those results:

Table 7. Outcomes of Subjects Who Withdrew Early From the Study

Urine Protein and eGFR	**Number of Subjects**	**Interpretation of Effect of Device on Disease Status**
No Follow-up Available	6	Cannot Determine
No Change in Urine Protein or eGFR	4	Disease Stabilization
Decrease in Urine Protein and increase in eGFR	3	Positive Response
Increase in Urine Protein and Decrease in eGFR	1	Disease Progression
No Change in Urine Protein and Decrease in eGFR	1	Likely Disease Progression

These outcomes are generally similar to that of the subjects that had full data available.

Safety

Primary safety endpoint: device-related and procedure-related serious adverse events (SAEs): The most common or serious adverse events with the Liposorber LA-15 system are listed in Table 7 below:

Table 8. Known Adverse Events Observed with the Liposorber LA-15 System

1. Death
2. Cardiac (including myocardial infarction)
3. Thrombocytopenia
4. Infection/bacteremia
5. Hypersensitivity (anaphylactoid) reaction
6. Nausea and vomiting
7. Reduction in Vitamin E level
8. Transient decrease in serum protein and albumin level
9. Hypotension
10. Flushing/blotching
11. Angina/chest pain
12. Fainting/lightheadedness
13. Anemia
14. Prolonged bleeding (at cannulation site)
15. Hemolysis
16. Device malfunction
17. Vertigo
18. Diaphoresis
19. Urticaria

As of the seven year report, eighty adverse events have been reported. Table 8 shows the most serious events that have been observed. The events include gastrointestinal (nausea/vomiting/diarrhea/abdominal pain/ache), fever/infection, upper respiratory symptoms, headache, edema/anasarca, lightheadedness/fainting, hypotension, anemia, malaise, and weakness. The sponsor posits and the agency agrees that these events are most likely related to the patients' underlying conditions and/or the requirement for a central venous catheter for vascular access.

Table 9. Summary Table of Major Adverse Events

Adverse Event Type	Number of Events	Relationship to Device
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	9	None
Fever/Infection	16	2 (Possible)
Upper Respiratory (Congestion/Pharyngitis)	8	None
Headache	7	None
Edema/Anasarca (Exacerbation)	4	None
Lightheadedness/Dizziness	3	None
Malaise	3	None
Hypotension	2	None
Leg cramps	2	None
Allergic reaction (mild)	2	None
Pancreatitis	2	None
Hyponatremia	1	None
Dehydration	1	None
Worsening of Nephrotic Syndrome	1	None
Pneumonia	1	None
Bacteremia	1	None
Anemia	1	None

Source: Based on data from H120005/R013 and R015

Secondary probable benefit endpoint: laboratory values, including eGFR. Laboratory values including estimated glomerular filtration rate (eGFR) by study visit are shown in Table 9 below. The table shows that among the fourteen subjects who completed full device treatment and had at least one post-treatment visit with laboratory results, eGFR was stable or increased in 12/14 (86%) subjects. Eleven of thirteen subjects (85%) displayed either stabilization or decline of urine protein (assessed by urine protein-to-creatinine ratio), while one subject does not have a follow-up value to assess. The evidence for these subjects shows a trend towards stabilization or improvement of laboratory indices.

Table 10. Renal Function (measured by estimated glomerular filtration rate) and other laboratory values by study visit

Subject	Baseline eGFR	Last eGFR	Trend in eGFR	Baseline U p/c	Last U p/c	Trend in U p/c
1	62	84	Increase	44	18	Decrease
2	89	79	Stable	8	6	Stable
3	85	100	Increase	6	0.4	Decrease
4	112	84	Decrease	2.6	N/A	Undetermined
5	171	109	Stable*	2	0.2	Decrease
6	60	34	Decrease	2	4	Increase
7	85	130	Increase	5	4	Stable
8	153	161	Stable	4	5	Stable
9	78	72	Stable	1	0.3	Decrease
10	159	160	Stable	27	15	Decrease
11	60	191	Increase	5	3	Decrease
12	216	131*	Stable	28	38	Increase
13	16	78	Increase	8	0.1	Decrease
14	58	117	Increase	29	3	Decrease

Source: Constructed from Table 2 of H120005/R017
*Baseline value was falsely elevated; follow-up value is normal for age

FDA Conclusions About Probable Benefit and Safety:
Conclusions remain limited due to the small number of subjects and a limited period of follow-up in many patients. For probable benefit, five of eleven (45%) of subjects had achieved either partial or complete remission one month after the last device therapy. In comparison, seven of eleven (64%) pediatric patients in the study by Hattori et al (Amer J Kidney Dis, 2003) showed either complete or partial remission one month after device therapy. Overall, the data show stabilization or improvement of eGFR over the follow-up period in the vast majority (86%) of patients, albeit a brief follow-up period for some patients. The rates and severity of adverse events have been relatively low considering the underlying patient risk profiles (chronic kidney disease with nephrotic syndrome) and the known risks associated with any extracorporeal therapy. The review team believes that the vast majority of adverse events were unrelated to the device, while two were possibly related. Enrollment has improved slightly; therefore, the study status has been changed to “Progress Adequate.” In summary, the post-approval study has not raised any new concerns regarding safety or probable benefit at this time. The study progress will continue to be monitored. FDA has worked interactively with the sponsor and study investigators to identify barriers to study enrollment that may be ameliorated by changes in study design.

LITERATURE REVIEW

Purpose

The purpose of this literature review is to keep current the knowledge published regarding the safety and effectiveness of Liposorber in pediatric patients for the treatment of nephrotic syndrome associated with primary focal segmental glomerulosclerosis.

Methods

FDA conducted a literature review of the pediatric use of Liposorber by Kaneka on January 4, 2021 including all publications written in English between January 1 to December 31, 2020 in PubMed, Embase and Google Scholar. Without any additional filters, the following search terms were used: Kaneka, Liposorber, Drug-resistant Pediatric Primary Focal Segmental Glomerulosclerosis, and LDL-Apheresis. A total of 37 articles were found. After reading the titles, abstracts, and full-texts, 11 articles were selected. However, 8 of these articles were later excluded because they only included adults or were non-systematic literature reviews.

Results

Summaries of the selected articles are included below.

Hothi DK and Fenton M (2020) The impact of home hemodialysis in children with severe cardiac failure. Hemodialysis International 2020; 24: E61–E66; DOI:10.1111/hdi.12872

Introduction

When faced with patients with deteriorating cardiac disease, nephrologists tend to accept that heart disease is unmodifiable and opting for stabilization. Likewise, cardiac patients with persistent renal failure are presented with a poor renal prognosis and prepared for renal transplantation.

This is a retrospective review of three dialysis-dependent children with moderate-to-severe cardiac failure in whom home hemodialysis normalized the cardiac function and restored renal function. One of the patients was treated with Liposorber but it is not clear if the other two patients were treated with Liposorber during Hemodialysis (HD).

Description of the Clinical Findings in the Patient treated with Liposorber

The patient presented at age 7 years with a history of bloody stools, weight loss, and abdominal pain. The patient was diagnosed with an ulcerative colitis-like inflammatory bowel disease. At age 8 years, he presented with nephrotic syndrome, which was steroid-resistant. A biopsy confirmed the collapsing variant of FSGS. Genetic screening was negative. He was treated with several immunosuppressants and Liposorber apheresis, but his renal function deteriorated. Upon starting hemodialysis (HD), he developed two episodes of posterior reversible encephalopathy syndrome (PRES), secondary to hypertension, triggering a decision to proceed bilateral nephrectomies. Post-operativley, he became increasingly hypotensive. Eight months later following a respiratory illness, he developed acute pulmonary edema. He was diagnosed with severe dilated cardiomyopathy and commenced on carnitine and intravenous milrinone, and his HD prescription was intensified to 3 to 4 hours, five to six times per week. His cardiac function

continued to deteriorate and thus he transitioned to a home HD (HHD) program, starting on 5 hours, five times per week. He was also commenced on sprinolactone and carvedilol owing to intradialytic tachycardia. After 7 months, he switched to a nocturnal program of 10 hours, five times per week.

He was admitted to hospital following a chest infection and mild pulmonary edema and was commenced on enalapril and digoxin; his HHD program was increased to 8 hours, 7 times per week, nocturnally. Over the following 12 months, his symptoms resolved, and his cardiac function gradually normalized with successful withdrawal of digoxin, enalapril and spironolactone

Conclusions
The article describes three children on dialysis with moderate-to-severe cardiac failure experiencing unexpected organ recovery with frequent HD, provided as HHD, and medical therapy. Pediatric patients receiving maintenance HD typically do not have epicardial disease unless there is severe, untreated uremia.

According to the authors, these cases highlight the medical benefits of frequent/HHD in severe cases of cardiac disease in patients with ESRD receiving HD.

Aljenedil S, Alothman L Belanger AM, Brown L, Lahijanian Z, Bergeron J, Couture P, Baass A, Ruel I, Brisson D, Khoury E, Gaudet D, Genest J, (2020) Lomitapide for treatment of homozygous familial hypercholesterolemia: The Quebec experience. Atherosclerosis 310 (2020) 54-63. 0021-9150/© 2020 Elsevier B.V.
https://doi.org/10.1016/j.atherosclerosis.2020.07.028

Background and Aims
Homozygous familial hypercholesterolemia (HoFH) is an orphan disease, most often caused by bi-allelic mutations of the *LDLR* gene. Patients with HoFH have elevated LDL-C levels >13 mmol/L, tendinmus xanthomata and severe, premature atherosclerotic cardiovascular disease (ASCVD). Untreated, most HoFH patients die of ASCVD in youth. New therapeutic modalities include lomitapide, an inhibitor of microsomal triglyceride transfer protein that lowers hepatic LDL-C production. The authors identified 79 Canadian patients with HoFH and describe their experience with lomitapide in 12 patients at the province of Quebec, a geographic area known to have a high prevalence of HoFH.

Methods
This is a retrospective case series of 12 patients with HoFH who were followed at three lipidology centers in the province of Quebec. Five (patients 1-5) patients were receiving extracorporeal LDL apheresis weekly or bimonthly at the lipid clinic of Quebec City, where two device systems were used: dextran sulfate (Liposorber LA-15, Kaneka, Japan) and Plasmat Futura system for Heparin Extracorporeal LDL Precipitation (HELP) system (B. Braun, Germany). However, it is not clear which of these five patients were treated with Liposorber and which ones were treated with HELP system.

Results
The Mean age of the patients was 44 ± 18 years; age at time of HoFH diagnosis ranged from 2 to 59 years. All patients were receiving a statin and ezetimibe 10 mg/day, and five patients were treated with LDL apheresis. Treatment with lomitapide reduced LDL-C levels by 38% (intention-to-treat). Intolerable gastrointestinal side effects were observed in three of twelve patients and were the main reason for treatment discontinuation. Three patients tolerated lomitapide at doses ranging between 5 and 30 mg/day without major side effects. Downwards drug titration was necessary in the 6 remaining patients because of gastrointestinal side effects (n = 5) and elevated liver enzymes (n = 1), and 2 of them finally discontinued treatment. In the present report, 5 patients were on LDL apheresis when lomitapide treatment was added, and they presented with side effects leading to down-titration of the dose, non-adherence and/or discontinuation. Consequently, the use of lomitapide did not modify the frequency of LDL apheresis, nor was this treatment withdrawn.

Conclusions
Lomitapide may be used to further decrease LDL-C in HoFH patients; gastrointestinal side effects and hepatic toxicity may limit adherence. However, in the five (5) patients that were on LDL apheresis when Lomitapide treatment was added, use of lomitapide did not modify the frequency of LDL apheresis, nor was the lomitapide discontinued.

Luirink IK, Hutten BA, Greber-Platzer S, Kolovoue GD, Dannf EJ, de Ferranti SD, Taylan C, Bruckert E, Saheb S, Oh J, Driemeyer J, Farnier M, Pape L, Schmitt CP, Novoa FJ, Maeser M, Masana L, Shahrani A, Wiegman A, Groothoff JW. Practice of lipoprotein apheresis and short-term efficacy in children with homozygous familial hypercholesterolemia: Data from an international registry (2020). Practice of lipoprotein apheresis and short-term efficacy in children with homozygous familial hypercholesterolemia: Data from an international registry. Atherosclerosis 299 (2020) 24-31. 0021-9150/ © 2020 Published by Elsevier B.V.T
https://doi.org/10.1016/j.atherosclerosis.2020.01.031

Background and Aims
HoFH may cause life-threatening atherosclerotic cardiovascular disease in childhood. Lipoprotein apheresis (LA) is considered a pivotal treatment option, but data on its efficacy, safety and optimal performance are limited. The authors developed an international registry to assess the outcomes of LA in HoFH children. In this article, the authors report LA policies and short-term outcomes.
Methods
The authors approached centers worldwide that were providing LA for children with HoFH for participation. The study included the collection of information on clinical and treatment characteristics on patients aged 0–19 years between November 2016 and November 2018.

Results
The study included 50 children, treated at 15 sites. Median (interquartile, or IQR) LDL-C levels at diagnosis, on medication and on LA were 19.2 (16.2–22.1), 14.4 (10.8–16.7) mmol/L and 4.6

mmol/L, respectively. Median IQR time between the diagnosis and start of LA was 2.8 (1.0–4.7) years. Six (12%) patients developed cardiovascular disease during that period. Most children received LA either weekly (43%) or biweekly (37%). Seven (17%) patients reached mean LDL-C levels<3.5 mmol/L, all of them treated at least weekly. Xanthomas were present in 42 (84%) patients at diagnosis and disappeared completely in 19 (45%) on LA. Side effects of LA were minor. There were significant differences in LA conduction between sites in terms of frequency, responsible medical specialties and vascular access.

Conclusions

The authors concluded that LA is a safe treatment and may effectively lower LDL-C in children with HoFH. However, there is room for improvement with respect to time of onset and optimization of LA therapy in terms of frequency and execution.

Highlights

The highlights of this investigation include the following:

- Lipoprotein apheresis (LA) is safe in children with HoFH with a paucity of side effects.
- LA leads to an important reduction of LDL-C and xanthomas in children with HoFH.
- Only a small number of children with HoFH reach treatment goals on LA.
- There are important differences in LA conduction strategies between different sites.

Summary of the Literature Review

The article by Hothi et al (2020) includes a retrospective study of three children receiving maintenance HD and moderate-severe cardiac failure in whom HHD normalized cardiac function and restored renal function. Among the three children described, one was receiving therapy with the Liposorber device system. The article found in this search shows encouraging efficacy of frequent HD to manage severe cardiac disease in chilren receiving HD.

The symptoms of the patient treated with Liposorber eventually resolved and his cardiac function gradually normalized with successful withdrawal of digoxin, enalapril and spironolactone.

The study by Aljenedil et al (2020) included five patients that were receiving LDL apheresis with either the Liposorber or Plasmat Futura system for Heparin Extracorporeal LDL Precipitation (HELP) system (B. Braun, Germany). When lomitapide treatment was added, some patients developed medication side effects requiring down-titration of the dose, non-adherence, or discontinuation of the medication. Consequently, the use of lomitapide did not modify the frequency of LDL apheresis, nor was LDL apheresis therapy discontinued.

The study by Luirink et al (2020) included an assessment of short-term efficacy of lipoprotein apheresis (LA) in 50 children with HoFH from an international registry. In patients treated once a week, LDL-C was lower than in patients treated once every two weeks. The majority of patients exhibited xanthomas at diagnosis, with disapperance of the lesions noted in almost half of the subjects at last follow-up on LA. Seven (17%) patients reached mean LDL-C levels<3.5 mmol/L. Side effects of LA were minor.

Conclusions of the Literature Review

FDA conducted a literature review of the pediatric use of Liposorber by Kaneka on January 4, 2021 including all publications written in English between January 1 to December 31, 2020 in PubMed, Embase and Google Scholar. A total of 3 articles were found to be pertinent during this time period.

These three articles found that lipoprotein apheresis using the Liposorber device leads to a clinically significant reduction of LDL-C and xanthomas in children. Additionally, Liposorber was found to be safe in children with a few side effects.

OVERVIEW OF MDR DATABASE

Strengths and Limitations of MDR Data
Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:

    - rare, serious, or unexpected adverse events;
    - adverse events that occur during long-term device use;
    - adverse events associated with vulnerable populations;
    - off-label use; and
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs and FDA's internal MDR database include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.

- Confirming whether a device caused a specific event can be difficult based solely on information provided in each report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Liposorber® LA-15 System

The MDR Database was searched on January 4, 2021 utilizing the following search criteria:

- Product codes: MMY (Lipoprotein, Low Density, Removal) and PBN (Apheresis for Focal Glomerulosclerosis in Pediatric Patients).
- Report Create Date: Between January 1, 2020 and December 31, 2020

The search resulted in five (5) MDRs: (2435151-2020-00001, 2435151-2020-00002, 2435151-2020-00003, 3002808904-2020-00005, and 3002808904-2020-00021) for the Liposorber® LA-15 system. Three (3) MDRs involve a pediatric patient. The other two (2) MDRs involve adult patients. All five MDRs reported serious injury events. All events occurred in the United States. Summary level information is provided below.

MDRs # 2435151-2020-00001 (Report Date: 18 December 2020) and # 3002808904-2020-00005 (Report Date: 21 February 2020):

Note: The events reported in the abovementioned MDRs are identical.

A 42-year-old male with familial hypercholesterolemia and hyper-Lp(a)emia was temporarily disconnected from Liposorber LA-15 System treatment to use the restroom. The patient's blood pressure decreased to 98/56 mmHg and the patient lost consciousness. The patient's blood pressure recovered to 124/68 mmHg, after which treatment with the Liposorber LA-15 System resumed. Treatment was discontinued at a plasma treatment volume of 3.8L despite an initial target volume of 4.45L.

The report listed the following concomitant medications: Lisinopril (ACE-inhibitor; withdrawn 6 days before the first LA-15 treatment), Plavix (antiplatelet drug), and Zetia (cholesterol lowering drug).

The reporter states that loss of consciousness was due to "a decrease in blood circulation in the body, and due to a rise in blood bradykin caused by gradual increase in plasma flow during the course of treatment." The reporter also cites the patient's "bad physical condition" as an additional potential cause for loss of consciousness.

This treatment was the patient's second with the Liposorber LA-15 System. During their first treatment two weeks prior, the patient experienced a mild decrease in blood pressure and felt faint and nauseous during treatment. The target plasma treatment volume of 4.4L was accomplished.

The reported event does not appear to be related to device function.

Fainting is a known risk associated with the Liposorber LA-15 System therapy, and the review team does not believe that a labeling change is required at this time.

The manufacturer submitted MDR 3002808904-2020-00005 and is aware of the event. Therefore, the review team believes that no follow up is required at this time.

MDR # 2435151-2020-00002 (Report Date: 18 December 2020):

Note: This MDR was reported in last year's PAC Executive Summary via MDR # 3002808904-2019-00005 (Report Date: 25 January 2019).

A 15-year-old boy with recurrent, post-transplant focal segmental glomerulosclerosis (FSGS) was receiving plasmapheresis until the day of event. The patient's estimated glomerular filtration rate (eGFR) was <60 and he was receiving ACEi (Enalapril). One of the catheter ports, per mother, was not working well. Only one of the ports was used for the plasmapheresis. Vital signs were stable at start of the treatment. Sixteen minutes into treatment the patient complained of chest pain, thrashed in the bed with lips cyanotic despite pulse oximetry of 100%. Oxygen was applied and 100 ml of normal saline was rapidly infused. A code was called, during which the patient received intravenous Solumedrol. Within five minutes, the patient improved and was transferred to the emergency department. There, he became stable after 30-40 minutes.

The events were most likely caused by bradykinin-release syndrome caused by an interaction between the ACEi and the LA-15 column. The current label requires withholding ACEi use within 24 hours of Liposorber device therapy. While this period is usually adequate to reduce the likelihood of bradykinin-release and hypotension, the medication half-life in this patient may have been longer due to reduced (eGFR <60 ml/min) renal function.

This event has been previously reported to the Agency via 3002808904-2019-00005, so no further action is necessary.

No labeling change is required as hypotension is a known side effect of Liposorber therapy.

MDR # 2435151-2020-00003 (Report Date: 18 December 2020) and # 3002808904-2020-00021 (Report Date: 23 November 2020):

Note: The events reported in the abovementioned MDRs are identical.

On 11/19/20, a 16-year-old patient with FSGS received a complete treatment with the Liposorber LA-15 System. After the treatment, at 4:00 p.m. on that day the patient was admitted to the hospital for anasarca with worsening acute kidney injury (AKI), the latter due to dehydration and elevated cyclosporine levels. On 11/22/20, the site reported s serious adverse event (SAE) and noted that the patient was still hospitalized. The report stated that the AE resolved on 11/24/20 and the patient would be continuing treatment with the Liposorber LA-15 System, but did not provide any further details about the course of the AKI.

The user facility reported that the actions taken to treat the AE included: temporary hold of cyclosporine and fluconazole therapy along with 25% albumin and oral/intravenous furosemide.

The site noted that the SAE was possibly related to treatment and that the device did not malfunction.

The patient had multiple risk factors for AKI, including cyclosporine (which causes renal vasoconstriction), dehydration, and possibly intravascular volume depletion due to hypoalbuminemia due to nephrotic syndrome, featured by anasarca. While the device can cause and the labeling includes the risk for hypotension (and therefore, reduced renal perfusion), it is unclear from the report if the patient developed hypotension during or immediately after Liposorber therapy.

No labeling change or further information is required since it is uncertain if hypotension occurred and may have contributed to the development of AKI, and, hypotension is a known potential risk associated with the device, as per the labeling.

VII. SUMMARY

FDA recommends:

1. Continued surveillance and will report the following to the PAC in 2022:
    - Annual distribution number
    - PAS follow-up results
    - Literature review
    - MDR review