

## LETTER TO THE EDITOR / ПИСМО УРЕДНИКУ

# Direct adsorption of LDL cholesterol – one center experience

#### Dear Editor,

Low-density lipoprotein (LDL)-apheresis is a method of extracorporeal elimination of the particles containing apolipoprotein B (ApoB)100. Table 1 lists the currently available LDL-apheresis techniques [1]. LDL-apheresis is applied in patients, where there has been no satisfactory reduction in lipoprotein levels, despite medical diet, physical activity, and the application of pharmacotherapy have been used [1].

### Table 1. LDL-apheresis techniques

HELP (Heparin-induced Extracorporeal LDL Precipitation)	The precipitation of ApoB by forming complexes with other proteins	
DALI (Direct Adsorption of Lipoproteins)	Positively charged ApoB binds to negatively charged polyacrylate anions	
Liposorber Dextran Sulfate	Positively charged ApoB binds to negatively charged dextran sulfate	
MONET	Lipoprotein size-based elimination	
TheraSorb	Filter columns containing ApoB antibodies	

LDL – low-density lipoprotein; ApoB – apolipoprotein B

The American Society for Apheresis guideline states the following indications for LDLapheresis: homozygous form of familial hypercholesterolemia (HoFH) with serum cholesterol level > 9 mmol/l or heterozygous form (HeFH) with LDL cholesterol level > 5.0 mmol/l [2, 3, 4].

The Dutch Lipid Clinic Network criteria is most frequently used for diagnosis familial hypercholesterolemia (FH) and consider: family history (severe HoFH, premature coronary artery disease), physical examination (e.g., tendon xanthoma), LDL-C levels and DNA mutation. Our center uses the Dutch Lipid Clinic Network criteria that are recognized by health care insurance system [5, 6].

Our center treats patients:

- with or without major adverse cardiac events (MACE),

 with the score of Dutch Lipid Clinic Network criteria ≥ 8, who do not achieve lowering LDL-C by more than 40% with the maximum tolerated dose of statin [4, 7].

The direct adsorption of lipoproteins (DALI) method reduces the total cholesterol by 54.1%, LDL-C by 62.3%, triglycerides by 52.3% and high-density lipoprotein (HDL)-C by 2.8% [8]. The appearance of the adsorber during the apheresis of a person with hyper-chylomicronemia is shown in Figure 1, while the appearance of a filter of a person without hyperchylomicronemia is shown in Figure 2. In Figure 1 is clearly seen an example of non-homogeneous adsorption in the filter, or inad-equate filter efficiency, caused by the blocking of pore with chylomicrones.

Within the Clinic for Endocrinology, there is an LDL-apheresis cabinet, which applies the



Figure 1. The appearance of the filter during the apheresis of a person with hyperchylomicronemia

**Received • Примљено:** October 17, 2021

Revised • Ревизија: September 5, 2022 Accepted • Прихваћено: September 12, 2022 Online first: September 15, 2022

#### Correspondence to:

Dragana TOMIĆ-NAGLIĆ Clinical Center of Vojvodina Clinic for Endocrinology, Diabetes and Metabolic Disorders Hajduk Veljkova 1–9 21000 Novi Sad Serbia dragana.tomic-naglic@mf.uns.ac.rs



Figure 2. The appearance of an adsorber during the apheresis of a person without hyperchylomicronemia

DALI method. In the past five-year period, 365 well-documented LDL-apheresis were performed. Based on this, a retrospective analysis of the results was made. The study has been approved by the local ethics committee and was conducted in accordance with the Helsinki Declaration. The results are presented in Table 2. [5, 9].

The results of treatment in our center, with a reduction of 67% in LDL-C and 62% in ApoB, coincide with data from retrospective studies, such as in Germany, which included 15,527 subjects [10].

The study by Schettler et al. [10] also showed a reduction of 78% in MACE. During the 5-year period of treatment in our center, there were no new MACE. This can be explained by the fact that the patients treated in our center were younger (average 54.81 years), and some of them without previous MACE, while Schettler et al. [10] presented the results of apheresis in patients with previous MACE, which are patients with higher cardiovascular risk, majority were women, in age range of 60–90 years. We considered

#### REFERENCES

- Stefanutti C, Julius U, Watts GF, Harada-Shiba M, Cossu M, Schettler VJ, et al. Toward an international consensus-Integrating lipoprotein apheresis and new lipid-lowering drugs. J Clin Lipidol. 2017;11(4):858-871.e3. [DOI: 10.1016/j.jacl.2017.04.114] [PMID: 28572002]
- Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apher. 2016;31(3):149–62. [DOI: 10.1002/ jca.21470] [PMID: 27322218]
- McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. J Am Heart Assoc. 2019;8(24):e013225. [DOI: 10.1161/JAHA.119.013225] [PMID: 31838973]

N = 365	Before apheresis	After apheresis	Reduction level after each treatment (%)
Total cholesterol (mmol/l)	13.6	6.41	56%
Triglycerides (mmol/l)	0.85	1.31	1€4%
LDL cholesterol (mmol/l)	6.49	2.11	67%
Non-HDL cholesterol (mmol/l)	7.16	2.66	63%
ApoA (g/l)	1.35	1.20	11%
ApoB (g/l)	1.64	0.62	62%

N- total number of procedures; LDL – low-density lipoprotein; HDL – high-density lipoprotein; ApoA – apolipoprotein A; ApoB – apolipoprotein B

the cumulative LDL-C level, and thus patients with HeFH undergo early interventions, which certainly contributes to better results in terms of MACE incidence [11].

We believe that there is insufficient awareness of the existence of familial HoFH [12–15]. Patients with FH have rapid progression of atherosclerosis with a high incidence of MACE. For this reason, strict control of lipid parameters is necessary in these patients [16–19].

Previous findings suggest that LDL-apheresis is an effective method of reducing LDL-C in those patients who do not achieve the target values with pharmacotherapy and lifestyle changes [20]. The method is well tolerated and, according to the previously published data, it stops the progression of atherosclerotic.

#### Conflict of interest: None declared.

Dragana Tomić-Naglić Mia Manojlović Milena Mitrović Jovana Prodanović Ivana Bajkin Slađana Pejaković University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; Clinical Center of Vojvodina, Clinic for Endocrinology, Diabetes, and Metabolic Disorders, Novi Sad, Serbia

- Thompson GR; HEART-UK LDL Apheresis Working Group. Recommendations for the use of LDL apheresis. Atherosclerosis. 2008;198(2):247–55. [DOI: 10.1016/j.atherosclerosis.2008.02.009] [PMID: 18371971]
- Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/ EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019;290:140–205. [DOI: 10.1016/j.atherosclerosis.2019.08.014] [PMID: 31591002]
- Schmidt EB, Hedegaard BS, Retterstol K. Familial hypercholesterolaemia: history, diagnosis, screening, management and challenges. Heart. 2020;106(24):1940–6. [DOI: 10.1136/heartjnl-2019-316276] [PMID: 32933999]
- 7. Özdemir ZN, Şahin Ü, Yıldırım Y, Kaya CT, İlhan O. Lipoprotein apheresis efficacy and challenges: single center experience.

Hematol Transfus Cell Ther. 2022;44(1):56–62. [DOI: 10.1016/j.htct.2021.01.009] [PMID: 33745887]

- Bulut M, Nisli K, Dindar A. The effect of DALI lipid apheresis in the prognosis of homozygous familial hypercholesterolemia: Seven patients' experience at a DALI apheresis center. Ann Pediatr Cardiol. 2020;13(2):111–6. [DOI: 10.4103/apc.APC\_56\_19] [PMID: 32641881]
- Campbell M, Humanki J, Zierhut H. A novel approach to screening for familial hypercholesterolemia in a large public venue. J Community Genet. 2017;8(1):35–44. [DOI: 10.1007/s12687-016-0285-1] [PMID: 27889901]
- Schettler VJJ, Neumann CL, Peter C, Zimmermann T, Julius U, Roeseler E, et al. The German Lipoprotein Apheresis Registry (GLAR) - almost 5 years on. Clin Res Cardiol Suppl. 2017;12(Suppl 1):44–9. [DOI: 10.1007/s11789-017-0089-9] [PMID: 28233268] Erratum in: Clin Res Cardiol Suppl. 2017 Jul 17.
- Korneva V, Kuznetsova T, Julius U. The Role of Cumulative LDL Cholesterol in Cardiovascular Disease Development in Patients with Familial Hypercholesterolemia. J Pers Med. 2022;12(1):71. [DOI: 10.3390/jpm12010071] [PMID: 35055385]
- Kayikcioglu M. LDL Apheresis and Lp (a) Apheresis: A Clinician's Perspective. Curr Atheroscler Rep. 2021;23(4):15. [DOI: 10.1007/ s11883-021-00911-w] [PMID: 33594522]
- Makino H, Koezuka R, Tamanaha T, Ogura M, Matsuki K, Hosoda K, et al. Familial Hypercholesterolemia and Lipoprotein Apheresis. J Atheroscler Thromb. 2019;26(8):679–87. [DOI: 10.5551/jat.RV17033] [PMID: 31231083]
- 14. Tromp TR, Hartgers ML, Hovingh GK, Vallejo-Vaz AJ, Ray KK, Soran H, et al; Homozygous Familial Hypercholesterolaemia

International Clinical Collaborators. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. Lancet. 2022;399(10326):719–28.

- [DOI: 10.1016/S0140-6736(21)02001-8] [PMID: 35101175]
  Taylan C, Weber LT. An update on lipid apheresis for familial hypercholesterolemia. Pediatr Nephrol. 2022.
  [DOI: 10.1007/s00467-022-05541-1] [PMID: 35467154] Online ahead of print.
- Tanaka A, Inaguma D, Watanabe Y, Ito E, Kamegai N, Shimogushi H, et al. Two Patients with Familial Hypercholesterolemia Who Were Successfully Weaned from Low-density Lipoprotein Apheresis after Treatment with Evolocumab. Intern Med. 2017;56(12):1531–5. [DOI: 10.2169/internalmedicine.56.7958] [PMID: 28626179]
- Ferreira L, Palma I, Bacelar C, Queirós JA, Madureira A, Oliveira JC, et al. Lipoprotein apheresis in the management of severe hypercholesterolemia and hyperlipoproteinemia(a)-The Portuguese experience. Transfus Apher Sci. 2018;57(5):676–80. [DOI: 10.1016/j.transci.2018.08.004] [PMID: 30287070]
- Thompson G, Parhofer KG. Current Role of Lipoprotein Apheresis. Curr Atheroscler Rep. 2019;21(7):26.
   [DOI: 10.1007/s11883-019-0787-5] [PMID: 31041550]
- Thompson GR. The scientific basis and future of lipoprotein apheresis. Ther Apher Dial. 2022;26(1):32–6.
   [DOI: 10.1111/1744-9987.13716] [PMID: 34331508]
- Duarte Lau F, Giugliano RP. Lipoprotein(a) and its Significance in Cardiovascular Disease: A Review. JAMA Cardiol. 2022;7(7):760–9. [DOI: 10.1001/jamacardio.2022.0987] [PMID: 35583875]