The 1st and the 2nd Italian Consensus Conferences on low-density lipoprotein-apheresis. A practical synopsis and update

Claudia Stefanutti

Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Immunohematology and Transfusion Medicine, Department of Molecular Medicine, "Sapienza" University of Rome, "Umberto I" Hospital, Rome, Italy

Abstract

The clinical indications and guidelines for low-density lipoprotein (LDL)-apheresis set by the 1st Italian Consensus Conference held in Ostuni in 1990 and completed in 1992, but never published, are reported schematically. In 1994, within the Project "Prevention and control of the factors of the disease (FATMA)" by the Italian National Research Council, subproject 8 "Control of cardiovascular disease", a "Hearing on therapeutic apheresis: need for a target-oriented project" was organised. The meeting was the last scientific initiative on LDL-apheresis supported by public funds in Italy. After roughly two decades of use of LDL-apheresis, new guidelines were required based on the latest scientific evidence. In 2006, the Italian multicentre study on LDL-apheresis Working Group (IMSLDLa-WP), a scientific initiative at national level, was developed. It initially gathered together 19 Italian centres qualified for the application of lipid apheresis and LDL-apheresis (2007-2008), then 23 in 2010, located in the north, south, centre of Italy and in Sicily and Sardinia. The multicentre study aimed to validate the protocol for selecting patients and to create a network between the Italian centres. A secondary objective was the creation of a database of patients with familial hypercholesterolaemia and other severe forms of dyslipidaemia undergoing treatment with LDL-apheresis using the available techniques. Since LDL-apheresis has multidisciplinary treatment indications, the agreement on the new guidelines was reached through a panel of experts, of different medical and surgical specialties, with scientific and medical interest in the treatment indications, application and development of LDL-apheresis. The initiatives of the IMSLDLa-WP led to the 2nd Italian Consensus Conference on LDL-apheresis held in Rome in 2009. The previous and most recent guidelines are reported here synoptically.

Keywords: Italian Consensus Conference on LDL-apheresis, lipoprotein apheresis, MTP inhibitor, mipomersen, PCSK9 inhibitors.

The 1st Italian Consensus Conference on LDL-apheresis (Ostuni, Italy, 1990)

Background - part one

The clinical criteria and guidelines for low-density lipoprotein (LDL)-apheresis set by the 1st Italian Consensus Conference, held in Ostuni in 1990, and completed in 1992, are reported in Table I. Given the scientific evidence collected in more than two decades of use of LDL-apheresis, updated guidelines are required. In 1994, within the Project "Prevention and control of the factors of the disease (FATMA)" by the Italian National Research Council, directed by Prof. Giorgio Ricci, a "Hearing on therapeutic apheresis: need for a target-oriented project" was organised[1]. The last scientific initiative on LDL-apheresis, of institutional relevance, financed with public funds, emerged from this meeting. The initiative was realised within subproject 8, "Control of the cardiovascular disease", directed by Prof. Cesare Dal Palù.

This meeting provided consensus on the following.

The patient to treat with LDL-apheresis

Introduction

- It has already been clearly demonstrated that LDL plasma concentration is one of the most important causes of atherosclerosis and subsequent cardiovascular complications, in particular, coronary complications. Patients affected by serious hyperlipoproteinaemia (often with a monogenic or polygenic basis) present with a history of previous

Table I - LDL-apheresis Interdisciplinary National Committee Guidelines (1990-1992).

The indications for treatment with LDL-apheresis are the following:

- Homozygous familial hypercholesterolaemia (FH) and double heterozygous FH: early start of therapy for all the patients.
- Primary hypercholesterolaemia: patients with at least two of the following needs for treatment:
  1) no response to multiple pharmacological therapies and dietary therapy;
  2) severe asymptomatic and symptomatic atheromasia, including previous acute myocardial infarction;
  3) coronary angioplasty, aortocoronary bypass, or other major vascular surgery, when pharmacological aids do not guarantee bypass patency with reasonable certainty;
  4) heart transplant.

© SIMTI Servizi Srl

All rights reserved - For personal use only
No other use without premission

coronary atherosclerotic disease (and/or carotid or peripheral disease), even in paediatric age; their rates of fatal and non-fatal coronary or cerebral events are between five to 100 times higher than those observed in the general population.
- It has also been confirmed that the increase of LDL and/or other variations of lipoproteins, such as very low-density lipoproteins (VLDL), b-VLDL and lipoprotein (a) in plasma can influence to varying degrees the progression of atherosclerotic lesions and clinical vasculopathy (microviscosity and fluid-dynamic characteristics of blood, endothelial integrity, cellular and immune system modulation, subendothelial lipid deposits, coagulatory effects, platelet activity and fibrinolysis, etc.).
- Numerous studies of statins indicate that a reduction in the mean level of total cholesterol and, in particular, that carried by LDL, causes a decrease in myocardial infarctions both in hyperlipoproteinaemic subjects as well as in the general population. In addition, very recent studies document the ability of these drugs to lead to the regression of atherosclerotic coronary lesions by reducing LDL-cholesterol plasma concentrations.

LDL-apheresis
- LDL-apheresis is a new procedure for selectively removing LDL from blood, which, briefly, is based upon the interaction of LDL with sub-layers capable of isolating atherogenic lipoproteins. LDL-apheresis is potentially applicable in the removal of other lipoproteins from blood [i.e. VLDL, Lp(a)].
- By means of LDL-apheresis it is possible to reduce plasma concentrations of LDL-cholesterol markedly, in a very brief time. During a 2- to 4-hour session up to 10 grams of LDL-cholesterol can be removed, reducing LDL-cholesterol levels by as much as 70-85%.
- Periodic repetition of apheresis sessions (possibly also combined with pharmacological therapy):
  a) maintains a mean LDL-cholesterol level much lower than that achieved with diet or drug therapy and,
  b) improves, in brief or even very brief time, the fluid-dynamic characteristics of blood. It is for this reason that this method is proposed as an option to prevent vascular complications of atherosclerosis, and also to interrupt the progression or initiate the regression of atherosclerotic lesions.
- Several methods are available to selectively remove various lipoproteins from plasma [LDL, VLDL, Lp(a)]: apheresis by means of monoclonal or polyclonal antibodies, attached to a fixed phase; selective apheresis by means of precipitation with sodium heparin; apheresis by means of chemical absorption, using dextrane sulphate or other absorbing chemicals; apheresis by means of semi-selective absorption on cellulose diacetate; and others as well.
- Selective methods for filtration include Liposorber® (dextransulphate on cellulose), the heparin-induced extracorporeal lipoprotein precipitation (HELP) system, and direct absorption of lipoprotein (DALI). Semi-selective filtration can be achieved via various systems for cascade filtration or double filtration. The Consensus group noted that severe hypertriglyceridaemia and hyperchylomicronaemia with associated acute pancreatitis can be treated by means of conventional, non-selective plasma-exchange.

Indications
- Homozygous or double heterozygous familial hypercholesterolaemia (FH).
- Heterozygous FH and other genetic hypercholesterolaemias, which meet at least one of the following criteria:
  - absence of response to diet and drug therapies;
  - presence of severe atherosclerosis;
  - patients with a coronary-aorta bypass or patients who have undergone major vascular surgery when the drug therapy does not guarantee stabilisation of the ischaemic heart disease.

Contraindications
- Paediatric age (with the exception of homozygous and double heterozygous FH).
- All the contraindications of extracorporeal therapies.
- Allergies to the anticoagulant class of drugs, which are simultaneously administered intravenously.
- Other factors to be considered contraindicative are: advanced age, other concomitant serious illnesses, the impossibility of evaluating other risk factors present, and the patient's refusal to follow other necessary therapies.

LDL-apheresis: where, how, and when it is to be performed
- LDL-apheresis must be performed in centres with medical competence in lipid and metabolic diseases, and with the ability to monitor the cardiovascular condition by invasive and non-invasive means. Laboratory centres that monitor atherogenic lipoprotein fractions should be available, and selective techniques of LDL-apheresis must be performed by clinicians who are experts in extracorporeal circulation.
- LDL-apheresis must be initiated only after appropriate diet and drug therapy has been attempted.
- During LDL-apheresis treatment, drug therapy and an appropriate diet must be continued.
- It is advisable to eliminate other notable risk factors, whenever possible, and cardiological assistance must

©SIMTI Service Srl

All rights reserved - For personal use only
No other use without premission

be guaranteed in order to evaluate positive or negative outcomes related to the extracorporeal treatment.
- Only methods that have been evaluated for sufficiently long periods of time, and which show no side effects to the lipoprotein profile, should be applied.
- A periodic evaluation of the tolerability of the treatment is recommended.
- Patients must make an informed decision to undergo treatment.

LDL-apheresis end results, timing of treatment and its suspension
- The primary objective of apheresis is the maintenance of the mean LDL-cholesterol at the lowest possible level.
- Since the increase in LDL-cholesterol after an LDL-apheresis treatment session varies among individuals (because of genetics, environmental factors, diet and drugs), the end result should be one that maintains the lowest possible LDL-cholesterol level for the individual patient, bearing in mind that all methods of prolonging times between sessions should be applied, so as to keep costs as low as possible, allow centres to treat more individuals, and reduce the burden of medical treatment for patients, etc.
- In patients with homozygous FH, and in the more serious cases, the timing of treatment should, in any case, be a session every 5-10 days (independently of the points raised in Section 6.2).
- Every 2-3 years a medical staff, consisting of experts, should evaluate the benefits of continuing treatment, based upon clinical and coronary outcomes as well as tolerance to treatment.
- The decision to suspend apheretic treatment needs to be made taking into account lipid, cardiological and transfusional issues, and also bearing in mind the patient's wishes.

The 2nd Italian Consensus Conference on LDL-Apheresis (Rome, Italy, 2009)

Background - part two

In 2006 the Italian Multicentre Study on LDL-apheresis Working Group (IMSLDLa-WP), led to the collection of 19 Italian centres in 2007 and 2008 (23 in 2010) qualified for the application of lipid apheresis and LDL-apheresis. These centres were located in the north, south, and centre of Italy and in the major islands, Sicily and Sardinia. Since LDL-apheresis has multidisciplinary treatment indications, agreement on the new guidelines was achieved through a panel of interdisciplinary experts, representing the different medical and surgical specialists with scientific and medical interest in extracorporeal treatment, and indications, application and development of LDL-apheresis techniques. The former guidelines of the LDL-apheresis Interdisciplinary National Committee were updated and in 2009 a 2nd Italian Consensus Conference on LDL-apheresis was held in Rome. The following research group, scientific societies, and patient association participated in the event and supported a consensus document later published in the international literature[2]: Italian Multicentre Study on LDL-apheresis Working Group (IMSDLa-WP), Metabolic Diseases and Atherosclerosis Study Group, Italian Society for the Study of Arteriosclerosis (*Società Italiana per lo Studio dell'Aterosclerosi*, SISA), Italian Society for Haemapheresis (*Società Italiana di Emaferesi e Manipolazione Cellulare*, SIdEM), Italian Society of Nephrology (*Società Italiana di Nefrologia*, SIN), Italian Society of Internal Medicine (*Società Italiana di Medicina Interna*, SIMI) and the Italian National Association for Familial Hypercholesterolaemia (*Associazione Nazionale Ipercolesterolemia Familiare*, ANIF).

This meeting provided consensus on the following.

The patient eligible for treatment with lipoprotein-apheresis

The diagnosis of severe dyslipidaemia must be clinical and genetic-molecular, and extended to first-degree relatives. The extension of xanthomatosis, if present, must be carefully evaluated. Early initiation of treatment with LDL-apheresis/lipid apheresis is indispensable to prevent severe malformations of the aortic valve and progression of atherosclerotic lesions in coronary arteries. Bearing this in mind, it is suggested that the treatment of children with homozygous FH starts from around 6 years of age. However, precocious symptoms and signs are to be considered warnings, which compel careful clinical and prognostic evaluation of each individual case. Clinically prominent indications may lead to earlier treatment with LDL-apheresis/lipid apheresis. Preliminary non-invasive and invasive investigations of cardiovascular profile must not be omitted before starting treatment with LDL-apheresis/lipid apheresis in homozygous FH subjects. The cardiovascular follow-up is evermore necessary in order to evaluate the efficacy and safety of the treatment over time, with particular reference to primary cardiovascular endpoints. Aortic and coronary catheterisation and/or high resolution computed tomography coronary angiography, must be carried out serially on a 2-yearly basis in patients with documented coronary and/or aortic valve lesions, or who have undergone revascularisation of the coronary arteries, or who are heading to aortic valve replacement[3-5]. The aorta and leg vessels may also be examined. Lp(a) is one of the variables co-related to lipid metabolism with prognostic value, and its assay is strongly suggested. Indications for apheresis to remove Lp(a) were considered. For detailed recommendations, see Tables II-VII.

© SIMTI Servizi Srl

All rights reserved - For personal use only
No other use without premission

Table II - LDL-apheresis in dyslipidaemias: clinical indications - 2nd Italian Consensus Conference on LDL-apheresis (2009).

- Homozygous familial hypercholesterolaemia (FH) and double heterozygous (compound) FH.
- Autosomal recessive FH.
- Heterozygous FH.
- Hyperlipoprotein(a)aemia.
- Severe non-FH hypercholesterolaemia associated with progressive coronary artery disease.
- Other genetically determined dyslipidaemias of atherogenic nature and high cardiovascular risk profile.

Table III - LDL-apheresis. Other suggested indications 2nd Italian Consensus Conference on LDL-apheresis (2009).

- Sudden loss of hearing.
- Cerebrovascular disease.
- Peripheral artery disease.
- Non-arteritic ischaemic optical neuropathy (NAION)[19-22].

Indications for LDL-apheresis in diabetes and pregnancy were also given.

Table IV - Clinical and diagnostic protocol in paediatric patients eligible for treatment with LDL-apheresis - 2nd Italian Consensus Conference on LDL-apheresis (2009).

The clinical and diagnostic protocol for paediatric patients, as for adults, must include:
- genetic-molecular diagnosis through molecular biology techniques;
- objective clinical examination with attention to lesions (xanthomas) related to dyslipidaemia;
- stress electrocardiography;
- echocardiography;
- echo colour Doppler of epi-aortic and ilio-femoral vessels;
- aortic and coronary artery catheterisation.

During the cycle of treatment the following are recommended:
- objective clinical examinations every 3 months;
- stress electrocardiography every 6 months;
- echocardiography every year;
- echo colour Doppler of epi-aortic and ilio-femoral vessels, every year;
- aortic and coronary artery catheterisation, every 2 years[4,23].

For paediatric patients, specialist paediatric and psychological support is indispensable. This should be foreseen at the beginning and during the entire cycle of treatment. It is also necessary to obtain written informed consent with authorising signatures by the parents.

Table V - Paediatric LDL-apheresis: indications and recommendations - 2nd Italian Consensus Conference on LDL-apheresis (2009).

- **Before starting LDL-apheresis** refractoriness to diet and combined cholesterol-lowering drugs (at reasonably high doses) must be proven; diagnosis and complete cardiovascular examination (including catetherisation) must be done.
- **Begin LDL-apheresis between 6 and 7 years of age (or before)**; a delay in starting LDL-apheresis (8-9 years) leads to the onset and progression of aortic valve disease.
- **Treatment with LDL-apheresis imposes achievement of the therapeutic target** (low density lipoprotein cholesterol <70 mg/dL - ATP III) in children at high cardiovascular risk.
- **Adverse reactions**
  Collateral effects of paediatric LDL-apheresis are rare if the procedure is carried out by a team of experts (understanding that apheresis doctors for adults are not necessarily experts in treating children).

Table VI - Cardiovascular examinations in patients under treatment with LDL-apheresis - 2nd Italian Consensus Conference on LDL-apheresis (2009).

- **Cardiovascular examination and electrocardiography:** must be performed before submitting patients to LDL-apheresis, and later at least once a year (follow-up) to evaluate the patient's clinical condition.
- **Cardiac echo colour Doppler**
  must be performed before submitting patients to LDL-apheresis, and later every 1-2 years (follow-up). In the case of documented lesions (left ventricular impairment, aortic supravalvular stenosis, and valvular insufficiency) the examination can be repeated more frequently.
- **Exercise electrocardiography**
  Performed to reveal the possible presence of objective findings suggestive of myocardial ischaemia that is not associated with angina or anginal equivalent; to be performed before submitting patients to LDL-apheresis and later once a year (follow-up). When indicated it can be substituted with stress myocardial scintigraphy, a pharmacologically-induced stress test, or stress echocardiography.

Table VII - Lipid apheresis in severe pancreatitis associated with severe hypertriglyceridaemia 2nd Italian Consensus Conference on LDL-apheresis (2009).

- **Methods**
  Both therapeutic plasmapheresis (plasma-exchange [PEX]) and cascade filtration can be used in hypertriglyceridaemic pancreatitis[11-13]. Comparing methods, the removal rate of triglycerides and chylomicrons is higher with plasma-exchange than with cascade filtration.
- **Treatment frequency**
  Usually a single therapeutic plasmapheresis or cascade filtration is sufficient to lower triglyceride levels and to improve a patient's clinical profile. The treatment should be started immediately after the symptoms of acute pancreatitis appear. In some cases a second treatment within 24 to 48 hours is recommended.
- **Treatment volume**
  1-1.5 plasma volumes.
- **Anticoagulants**
  Many studies used ACD-A. Some authors suggest the use of heparin as it induces the release of lipoproteinlipase from the endothelium, increasing the removal of triglycerides. On the other hand, heparin could worsen pancreatic haemorrhages and, therefore, its administration is much debated and still controversial.
- **Substitution fluids**
  Albumin is frequently used as well as fresh frozen plasma as its lipoproteinlipase content would enhance the removal of triglycerides.

Discussion and conclusions

The conclusions of the first two Italian Consensus Conferences on LDL apheresis are presented here. The treatment of patients with severe dyslipidaemia is a fast evolving field. It is, therefore, necessary to update the guidelines continuously. This article is a review and summary of the most relevant aspects of the 1st and the 2nd Italian Consensus Conferences on LDL-apheresis (1990-2009). Synoptic tables with statements that can be used in clinical practice are presented. The statements

© SIMTI Servizi Srl

All rights reserved - For personal use only
No other use without premission

reported reflect the available evidence and were made according to objective criteria.

Recent international updates on the management of dyslipidaema include guidance on the use of lipoprotein apheresis. For example, the National Lipid Association (NLA) recommendations for the management of dyslipidaemia include, for the first time in the USA, a statement that LDL-apheresis may be considered *"For selected patients with severe hypercholesterolemia"*[6]. Table VIII shows the NLA Expert Panel on FH criteria for consideration of LDL-apheresis, together with the Food and Drug Administration (FDA)-approved indication. The authors noted that the NLA criteria are more inclusive than the FDA-approved indication criteria, which has potential implications for clinicians with regards to reimbursement.

A recent position paper on homozygous FH by a Consensus Panel of the European Atherosclerosis Society also recommended that, where available, lipoprotein apheresis is an important adjunctive treatment for homozygous FH[7]. Specifically, the Consensus Panel recommended that lipoprotein apheresis should be initiated as early as possible, ideally before the age of 5 years and not later than the age of 8 years, but acknowledged that *"this and the frequency of treatment represent a compromise between access to centres, the severity of the disease, affordability, and the patient's choice"*[7].

Recent developments in relation to the novel lipid-lowering agents are promising and suggest the need for new studies to investigate forms of combination treatment with lipoprotein apheresis. A number of novel agents with different mechanisms of action may offer further treatment options for patients with severe dyslipidaemia, including homozygous FH (Table IX).

Lomitapide, an oral inhibitor of microsomal triglyceride transport protein (MTP), is approved for use in 35 countries, including the European Union, the USA, Canada, Mexico, Taiwan and Israel, as an adjunct to a low-fat diet and other lipid-lowering therapies including LDL-apheresis, in the treatment of patients with homozygous FH[8,9]. When added to a low-fat diet and ongoing standard lipid-lowering treatment including apheresis, lomitapide has been shown to significantly reduce LDL-cholesterol in adult patients with homozygous FH to a similar extent irrespectively of whether or not the patient is receiving concomitant apheresis[10]. Mipomersen, an injectable antisense inhibitor of apo B synthesis is approved in the USA as an adjunct to lipid-lowering medications and diet in patients with homozygous FH but its use as an adjunct to LDL-apheresis is not currently recommended[11].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to be effective in the treatment of FH[12,13]. Evolocumab, a monoclonal antibody to PCSK9, was recently approved by the European Commission for the treatment of patients with homozygous FH, hypercholesterolaemia and mixed dyslipidaemia, including those on apheresis[14]. Another PCSK9 inhibitor, alirocumab, is approved for use in the USA and the European Union as an adjunct to diet and statin therapy for adults with heterozygous FH or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol[15]. The prescribing information for alirocumab does not specifically mention its use in patients undergoing apheresis[15]. At least for now, there is no specific clinical trigger for adding these agents to apheresis, and clinical decisions of this type lie between the doctor and the patient.

Table VIII - National Lipid Association criteria for consideration of LDL-apheresis (adapted with permission from Jacobson *et al.*, J Clin Lipidol 2014)[6].

NLA criteria from expert panel on FH	FDA-approved indication
LDL-apheresis may be considered for the following patients who, after 6 months, do not have an adequate response to maximum tolerated drug therapy: - Functional homozygous FH with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL). - Functional heterozygous FH with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) and no or one risk factor. - Functional heterozygous FH with LDL-C ≥200 mg/dL (or non-HDL-C ≥230 mg/dL) and high risk characteristics, such as two risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay. - Functional heterozygous FH with LDL-C ≥160 mg/dL (or non-HDL-C $190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).	LDL-apheresis is considered medically necessary when patients have failed diet and maximum drug therapy from at least two separate classes of lipid-lowering drugs for at least 6 months in addition to any one of the following criteria: - Homozygous FH with LDL-C ≥500 mg/dL. - Heterozygous FH with LDL-C ≥300 mg/dL. - Functional heterozygous FH with LDL-C ≥200 mg/dL in patients with coronary artery disease.

CHD: coronary heart disease; FDA: Food and Drug Administration; FH: familial hypercholesterolaemia; LD: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; NLA: National Lipid Association; non-HDL-C: non-high-density lipoprotein cholesterol.

© SIMTI Servizi S.r.l.

All rights reserved - For personal use only
No other use without premission

Table IX - Novel drug treatments for severe dyslipidaemia.

Name	Mechanism of action	Use with apheresis?
Lomitapide	Oral inhibitor of MTP	Yes[8,9]
Mipomersen	Antisense inhibitor of apo B synthesis	Not recommended[11]
Evolocumab	Monoclonal antibody to PCSK9 (approved for treatment of adults)	Yes[14]
Alirocumab	Monoclonal antibody to PCSK9	Not mentioned in USA prescribing information[15]

MTP: microsomal triglyceride transport protein; PCSK9: proprotein convertase subtilisin/kexin type 9.

When considering any new therapeutic approach, it will be important to take into account the effects of the various novel lipid-lowering agents not only on plasma lipid and lipoprotein levels, but also on the endothelium and on inflammation in general. Recent studies have suggested that lipoprotein apheresis may favourably influence regression of atherosclerotic lesions through effects unrelated to the extracorporeal removal of lipoproteins, such as the decrease of inflammatory mediators[16-18]. In some cases firm conclusions are difficult to draw, but the available evidence, although limited, remains the only concrete conclusion that can guide the clinician. Our concern is that the lack of collaboration between medical device and pharmaceutical companies will greatly affect the real opportunities of conducting studies in this field as the overwhelming cost of such studies is beyond the reach of investigators. Nevertheless, the most evident conclusion is that appropriate therapy in the patient with severe dyslipidaemia is one that reduces LDL-cholesterol and Lp(a) and thwarts the development of atherosclerotic lesions leading to severe ischaemic complications. For the aforementioned reasons we have developed this set of recommendations to guide the experts who take care of patients deserving a correct, continuous and combined therapeutic approach. These recommendations, together with recent international statements on the management of dyslipidaemia, provide clinicians with guidance on which patients are most likely to benefit from lipoprotein apheresis. As different centres use different apheresis techniques and schedules, a European Consensus statement providing further detailed guidance on the use of specific apheresis techniques and treatment protocols, including their use in combination with different pharmacotherapies, would be of great value in the future.

The Author declares no conflicts of interest.

References

1) Stefanutti C, Vivenzio A, Di Giacomo S, et al. In: Progetto finalizzato. Prevenzione e controllo dei Fattori di Malattia - FATMA. L'aferesi terapeutica: necessità di ricerca finalizzata. Hearing. Rome, October 28, 1994. Proceedings. October 28, 1994; Rome. [In Italian.]
2) Stefanutti C. The 2009 2nd Italian Consensus Conference on LDL-apheresis. Nutr Metab Cardiovasc Dis 2010; **20**: 761-2.
3) Mollet NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation 2005; **112**: 2318-23.
4) Stefanutti C, Vivenzio A, Di Giacomo S, et al. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion 2009; **49**: 1461-70.
5) Kazakauskaite E, Husmann L, Stehli J, et al. Image quality in low-dose coronary computed tomography angiography with a new high-definition CT scanner. Int J Cardiovasc Imaging 2013; **29**: 471-7.
6) Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol 2014; **8**: 473-88.
7) Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; **35**: 2146-57.
8) Aegerion Pharmaceuticals Inc. Lojuxta summary of product characteristics. 2013. Available at: https://www.medicines.org.uk/emc/medicine/28321/SPC/Lojuxta+hard+capsules/. Accessed on 20/03/2016.
9) Aegerion Pharmaceuticals Inc. Juxtapid prescribing information. 2013. Available at: http://www.juxtapid.com/sites/default/files/downloads/Prescribing_Information.pdf. Accessed on 20/03/2016.
10) Stefanutti C, Blom DJ, Averna MR, et al. The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia - a post-hoc analysis of a phase 3, single-arm, open-label trial. Atherosclerosis 2015; **240**: 408-14.
11) Genzyme Corporation. Kynamro prescribing information. 2013. Available at: http://www.kynamro.com/~/media/Kynamro/Files/KYNAMRO-PI.pdf. Accessed on 20/03/2016.
12) Farnier M. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolaemia not adequately controlled with current lipid-lowering therapy: results of ODYSSEY FH I and FH II studies. European Society of Cardiology; 2014; Barcelona, Spain.
13) Stein EA, Giugliano RP, Koren MJ, et al. Efficacy and safety of evolocumab (AMG 145), a fully human monoclonal antibody to PCSK9, in hyperlipidaemic patients on various background lipid therapies: pooled analysis of 1359 patients in four phase 2 trials. Eur Heart J 2014; **35**: 2249-59.
14) Amgen L. Repatha summary of product characteristics. 2015. Available at: https://www.medicines.org.uk/emc/medicine/30627. Accessed on 20/03/2016.

All rights reserved - For personal use only
No other use without premission

15) Regeneron, Sanofi. Praluent prescribing information. 2015. Available at: http://www.regeneron.com/Praluent/Praluent-fpi.pdf. Accessed on 20/03/2016.
16) Zenti MG, Stefanutti C. Effects of selective H.E.L.P. LDL-apheresis on plasma inflammatory markers concentration in severe dyslipidemia:iImplication for anti-inflammatory response. Cytokine 2011; **56**: 850-4.
17) van Wijk DF, Sjouke B, Figueroa A, et al. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. J Am Coll Cardiol 2014; **64**: 1418-26.
18) Eliaz I, Weil E, Dutton JA, et al. Lipoprotein apheresis reduces circulating galectin-3 in humans. J Clin Apheresis 2016; **31**: 388-9.
19) Suckfull M, Group. HLS. Fibrinogen and LDL apheresis in treatment of sudden hearing loss: a randomised multicentre trial. Lancet. 2002; **360**: 1811-7.
20) Jeynes B, Provias J. Evidence for altered LRP/RAGE expression in Alzheimer lesion pathogenesis. Curr Alzheimer Res 2008; **5**: 432-7.
21) Kobayashi S. Applications of LDL-apheresis in nephrology. Clin Exp Nephrol 2008; **12**: 9-15.
22) Thompson GR, Heart-UK LDL Apheresis Working Group. Recommendations for the use of LDL apheresis. Atherosclerosis 2008; **198**: 247-55.
23) Koga N, Iwata Y, Yamamoto A. Angiographic and pathological studies on regression of coronary atherosclerosis of FH patients who received LDL-apheresis treatment. Artif Organs 1992; **16**: 171-6.

Arrived: 15 October 2015 - Revision accepted: 12 January 2016
Correspondence: Claudia Stefanutti
Molecular Medicine - Extracorporeal Therapeutic Techniques, Lipid Clinic and Atherosclerosis Prevention Centre
Immunohematology and Transfusion Medicine Unit
Sapienza University of Rome
Viale del Policlinico 155
00161 Rome, Italy
e-mail: claudia.stefanutti@uniroma1.it

© SIMTI Servizi Srl

All rights reserved - For personal use only
No other use without premission