consensus report

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Lipoprotein-apheresis: Austrian consensus on indication and performance of treatment

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Summary The prevalence of familial disorders of lipid metabolism in Europe is higher than believed so far. In severely affected patients in whom conventional combined lipid lowering agents are insufficient to achieve target values, patients being intolerant to all the available members of the statin family as well as in patients with elevated lipoprotein(a) (100 mg/dl) and progression of atherosclerotic vascular disease, despite even normal low-density lipoproteins (LDL)-cholesterol values, lipoprotein-apheresis treatment is indicated. The Austrian Apheresis Consensus compares the inclusion criteria for patients to be treated in Austria with those from Italy, Germany, Spain, Japan, UK and the United States. The cut off level of 100 mg/dl for lipoprotein(a) is higher in Austria as compared to the aforementioned countries (50 or 60 mg/dl, respectively). The available clinical data reveal that regular weekly lipoprotein apheresis not only results in a significant lowering of the respective atherogenic lipid and lipoprotein parameters, but also in a significant decrease in clinical events and interventions. The underlying mechanisms such as non-lipid effects, side effects as well as the different available treatment principles are compared. For patients meeting the inclusion criteria, lipoprotein apheresis is a safe and effective therapy significantly reducing vascular events.

Keywords Lipoprotein-apheresis · Familial hypercholesterolemia · Lipoprotein(a) · Austrian consensus · Vascular events

Introduction

Familial hypercholesterolaemia (FH) is a consequence of gene mutations of the receptor for low-density lipoproteins (LDL), the mutations being localised on chromosome 19 [1]. More than 700 different mutations may cause defects in the LDL-receptor. The extent of the defect is responsible for the severity of the metabolic disturbance [2]. The most severe form is associated with a complete absence of receptors; but also a loss of function defect may occur. As a consequence the hepatic uptake and lysosomal degradation of LDL-cholesterol (LDL-C) is disturbed [3]. While homozygous FH has been reported to have a prevalence of 1:1,000,000 [4], new data suggested a much higher prevalence of 1:150,000, similarly the prevalence of heterozygous FH has been estimated to be 1:500 but recent data suggest about 1:150, according to newest results from the Netherlands (Kastelein and Hovingh, personal communication, 2014). In certain populations the incidence of the disease is higher due to a genetic founder effect, for example in French Canadians, South Africans, Lebanese and Finns [5–7]. This has to be considered in immigrants from these regions. There is a gene dose effect that means that homozygous patients exhibit significantly higher LDL-C levels as compared to

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heterozygous individuals. In homozygous FH patients LDL-C levels of > 400 mg/dl to > 1000 mg/dl are measured while in heterozygous of > 250 mg/dl [8]. LDL-C values of > 300 mg/dl in children imply a homozygous FH.

Affected individuals, show a higher rate of cardiovascular diseases, starting often at early age. The onset of cardiovascular disease is usually earlier in affected males as compared to females. In homozygous patients cardiovascular events occur very early, the age of onset is around 10 times earlier than in heterozygous FH. Myocardial infarction in children with homozygous FH has been already reported at the age of 4–5 years, while in heterozygous individuals events most frequently start between the age of 40–50 years. Typical clinical symptoms such as skin and tendon xanthomas are much more frequent in homozygous FH, they may, however, be absent in about 20–30 % of patients with proven FH [9]. The prevalence of arcuslipoides ranges around 30 %, but is not necessarily associated with a lipid metabolism disorder.

First step of treatment are always lifestyle measures but they mostly show little effect in FH and almost never result in a normalization of lipid levels. Statins, which competitively inhibit the 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, are the primary drug treatment of choice usually at high doses [10]. This enzyme is rate limiting for cholesterol biosynthesis. As a consequence of the inhibition, LDL-C is reduced [11]. As a result, the expression of hepatic receptors is increased removing additional LDL-C out of the circulation. The efficacy of statin treatment therefore is particularly dependent on functionally intact LDL-receptors. Furthermore, statins inhibit the hepatic synthesis of apolipoprotein B-100 and reduce the synthesis and secretion of triglyceride-rich lipoproteins [12]. In summary, an increased hepatic uptake is the primary mechanism of the LDL-C reduction by statins; furthermore, also the reduced hepatic production and secretion of lipoproteins play a role [13]. The clinical efficacy of statin therapy with an improved prognosis and a decrease in mortality has been well documented in various patient populations [14]. A recent meta-analysis of 25 randomized studies with more than 170,000 patients has also documented the effectiveness and safety of a more intensive LDL-C lowering [15]. As a consequence of a LDL reduction of 1.0 mmol/l, the annual cardiovascular event rate was reduced by a fifth [15]. Large cohort studies underline that statin therapy even in patients with FH are lowering cardiovascular event rates significantly [16, 17].

In case statin monotherapy is insufficient a combination treatment with resorption inhibitors like colestyramin and ezetimibe is indicated, although endpoint studies are still lacking with these therapies. Colestyramin (Quantalan®) and colsevelam (Cholestagel®) are inhibitors of bile acid resorption with a compensatory increased bile acid synthesis and result in a decrease in hepatic LDL-reserve. Consequently, augmented circulating LDL-cholesterol can be taken up by the liver. Ezetimibe is inhibiting the intestinal uptake of cholesterol. Lipoproteins in the blood are decreased resulting in an increased expression of hepatic LDL-receptors and increased uptake of circulating LDL by the liver.

The addition of resorption inhibitors or ezetimibe to statin treatment actually results in a further reduction of LDL-C by 15–20 % [18–20]. In rare cases with additionally elevated triglyceride values a combination with high-dose omega-3-fatty acids is meaningful [21].

If all standard therapeutic modalities with maximally tolerated lifestyle modification and combined drug treatment are insufficient to achieve lipid goals, lipoprotein (Lp)-apheresis is indicated. The mechanism of action is an extracorporeal selective elimination of atherogenic lipoproteins. The term LDL-apheresis used in the past has been replaced by the term Lp-apheresis as beside LDL-C also other atherogenic lipoproteins, in particular Lp(a), are eliminated by the treatment.

In the following an overview of indications, methods, patients care and special aspects of this therapeutic modality are presented.

Indications

The indications for Lp-apheresis in patients with homozygous FH or therapy resistant heterozygous FH patients in Austria are summarized in Table 1.

For comparison Table 2 shows the indications for Lp-apheresis in other countries such as Germany, UK, Italy, Japan, Spain and the USA.

This comparison demonstrates that the proposed indication in Austria (Table 1) is comparable; only for Lp(a) after intensive discussion a cut-off value of 100 mg/dl (as compared to 60 and 50 mg/dl in Germany, UK, Italy and USA, respectively) has been determined. Calculations from the USA suggest, that Lp-apheresis is necessary in about 1 out of 20,000 people [27]. In this calculation the indications of elevated Lp (a) and statin intolerance, however, are not included.

As already mentioned in patients with homozygous FH—depending on the extent of the defect—excessive hypercholesterolemia with severe atheromatous vascular lesions and premature cardiovascular events is already frequent in childhood. Treatment with lipid-lowering drugs at a maximal tolerated dose should be initiated in specialized centres. Initiation of Lp-apheresis therapy in primary prevention is already recommended in childhood [22]. A vascular risk assessment according to the usual risk charts (e.g. Framingham score) is contraindicated in homo- and heterozygous individuals, as these charts significantly underestimate the respective risk [26]. In contrast, in all patients with suspicion of FH extensive lipidological, cardiological and angiological examination is required in order to eventually discover a premature clinically manifested atherosclerosis (coronary heart disease (CHD), peripheral vascular disease (PVD), cerebrovascular disease (CVD)). If the clinical symptoms and/or the atherosclerotic process documented by any imaging modality show progression with an LDL-cholesterol of > 130 mg/dl (see Table 1) [28] Lp-

Table 1 Indications for Lp-apheresis

Primary prevention
Homozygous FH (Start of treatment in childhood)
Severe heterozygous FH if LDL-C > 190 mg/dl[a]
Secondary prevention
FH if LDL-C > 160 mg/dl[a]
FH if LDL-C > 130 mg/dl[a] and documented *progression* of clinically manifested *atherosclerosis*
Documented intolerance to all the available statins due to side effects and not reaching LDL-C treatment goals
Lp(a) > 100 mg/dl (even if total cholesterol and LDL-C are in the normal range) and documented *progression* of atherosclerosis

LDL-C low-density lipoproteins-cholesterol, *FH* Familial hypercholesterolaemia, *Lp(a)* lipoprotein apheresis
[a]despite maximal tolerated lifestyle modification and combined drug treatment

apheresis is indicated. In the recent past particularly two groups of patients have been admitted for Lp-apheresis, on the one hand patients not achieving the LDL-goals as a consequence of an intolerance to all the available statins, on the other hand patients with severe elevation of Lp(a), even with total and LDL-cholesterol levels within the normal range.

Lp-apheresis is performed in specialized centres after appropriate full information of the patients and obtaining a written informed consent. The initiation of treatment usually starts before the age of 60 years except in some special cases. It is a life-long therapy usually performed in weekly intervals. This type of treatment requires a high compliance of the patient, therefore a detailed full information is required in advance. During pregnancy statins are contraindicated, but Lp-apheresis has to be continued [29]. In case of onset of neoplastic or other severe diseases an individual decision with the respective caring physician is required in order to decide, whether the Lp-apheresis should be continued or not. As repeatedly mentioned, dietary restrictions, a maximally tolerated lipid lowering medication as well as a regular control and therapy of additional cardiovascular risk factors are necessary in all patients. Particular attention has to be drawn to the fact that the patients do not gain weight during therapy. Ideally, patients obtain a concomitant dietary counselling. For the initiation of treatment on an outpatient basis an approval from the respective insurance to cover the costs has to be obtained in advance.

Therapeutic efficacy

a. Metabolic control

For the therapeutic decision a complete assessment of lipid and lipoprotein parameters including the measurement of total cholesterol, LDL-C, HDL-C, triglycerides as well as Lp(a) is necessary.

The acute lowering of apoB containing lipoproteins (LDL-C, Lp(a), VLDL) is dependent on the efficacy of the system used and the treated blood/plasma volume. Most apheresis systems exhibit a comparable efficacy of > 70 % [30]. In parallel HDL-C is also lowered by 5– 25 % [31].

During the first days after the Lp-apheresis treatment a fast rebound of LDL-C and Lp(a) is observed, followed by a somewhat slower increase later on; the pre-values are achieved again after about a week. Repeated regular treatment can avoid a complete Lp(a) recovery. Lp-apheresis is also stimulating the expression of the LDL-receptors, inducing an additional lipid lowering effect [32]. After about 4–6 treatments a new somewhat lower mean-value under treatment is achieved due to receptor regulation. The mean cholesterol and LDL-C values in the interval between the treatments can be calculated according to the formula ($C_{med} = C_{min} + 0.73(C_{max} - C_{min})$) [33]. Alternatively, in clinical routine, the arithmetic mean between the pre- and post-values is frequently used. Recently, the following therapeutic goals for patients with homozygous FH have been recommended [34]:

- Acute reductions of total cholesterol ≥ 65 % or LDL-C ≥ 70 % after each treatment, respectively;
- A pre-value of total cholesterol < 350 mg/dl (< 9 mmol/l) for the next treatment or a lowering of more than 50 % from the initial value before the treatment with Lp-apheresis, i.e. LDL-C < 330 mg/dl (< 8,5 mmol/l) or a lowering of more than 55 % from the pre-value before initiation of Lp-apheresis treatment;
- In patients with heterozygous FH that is refractory to pharmacotherapy, the target in the interval between the treatments is a mean LDL-C ≤ 100 (≤ 2.6 mmol/l) or a lowering of ≥ 60 % from the pre-value before Lp-apheresis initiation [25].

During continuous regular Lp-apheresis-treatment beside the lowering of LDL-C and Lp(a) also other beneficial effects such as a reduction of markers of oxidative stress, inflammation, adhesion molecules and platelets, as well as an improvement in haemorheology (e.g. lowering of fibrinogen) due to unspecific removal of coagulation factors have been demonstrated (see Table 3) [35–42].

b. Cardiovascular events

Clinical-therapeutic efficacy aims at a reduction of the high cardiovascular morbidity and mortality. The lowering of LDL-cholesterol or the change in morphological and functional parameters (i.e. coronary stenosis, Doppler index in PAD, carotid artery stenosis) are potent surrogate markers for the evaluation of treatment. Finally, a relevant decrease in cardiovascular events is the aim of the treatment.

After a single Lp-apheresis improved cerebral perfusion has been reported, while a repeated (6 times) therapy resulted in an increased reactive hyperemia in peripheral vessels [43, 44]. These results have been interpreted as a sign of improved endothelial function

Table 2 Lp-apheresis guidelines in different countries

Country	Guideline
Germany: Richtlinie des Gemeinsamen Bundesauschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung, 2013	*Homozygous FH*
	Severe hypercholesterolemia, if LDL-C cannot be sufficiently lowered despite a 12-months documented maximal dietary and drug treatment
	Lp(a) > 60 mg/dl and LDL-C in normal range with progression of cardiovascular disease (CHD, PVD, CVD) documented clinically and by any imaging modality
United Kingdom: Heart-UK LDL Apheresis Working Group, 2008 [22]	*Homozygous FH*, if patient > 7 years and total cholesterol > 350 mg/dl or < 50 % decrease despite drug treatment
	Heterozygous FH and progression of CHD if LDL-C > 200 mg/dl or < 40 % decrease despite maximal drug treatment
	Lp(a) > 60 mg/dl and progression of CHD if LDL-C > 125 mg/dl despite maximal drug treatment
Italy: 2009 [23]	*Homozygous FH*
	Heterozygous FH and progression of CHD insufficient LDL-C lowering despite maximal drug treatment or statin intolerance
	Lp(a) > 60 mg/dl with a *high cardiovascular risk* and positive family history for premature CHD or *documented progression of CHD*
	Severe hypercholesterolemia (non-FH) and progression of CHD
Japan: 2012 [24]	*Homozygous FH*
	Heterozygous FH if LDL-C > 400 mg/dl under a low-fat diet or > 250 mg/dl during statin treatment in CHD, respectively
Spain: International Panel on Management of FH, 2004 [25]	*Heterozygous FH* and symptomatic CHD, if LDL-C > 160 mg/dl or lowering < 40 % despite maximal drug treatment
USA: National Lipid Association, 2011 [26]	*Functional homozygous FH* if LDL-C ≥ 300 mg/dl (or non-HDL-C ≥ 330 mg/dl)
	Functional heterozygous FH if LDL-C ≥ 300 mg/dl (or non-HDL-C ≥ 330 mg/dl) and 0–1 additional risk factors
	Functional heterozygous FH if LDL-C ≥ 200 mg/dl (or non-HDL-C ≥ 230 mg/dl) and ≥ 2 additional risk factors or Lp(a) ≥ 50 mg/dl;
	Functional heterozygous FH if LDL-C ≥ 160 mg/dl (or non-HDL-C ≥ 190 mg/dl) and high risk characteristics (i.e. cardiovascular disease or diabetes). For all patients an insufficient response to maximal drug treatment after 6 months is required

LDL-C low-density lipoproteins-cholesterol, *FH* Familial hypercholesterolaemia, *CHD* coronary heart disease, *PVD* peripheral vascular disease, *CVD* cerebrovascular disease, *Lp(a)* lipoprotein(a)

after Lp-apheresis. After 2 years of therapy a significantly improved regional myocardial perfusion in myocardial scintigraphy and an improved left ventricular ejection fraction have been shown [45]. Also a reduction of symptoms of angina pectoris, an improved walking distance in intermittent claudication, a regression of coronary atherosclerotic lesions—assessed by means of angiography or intravascular sonography, respectively—and a decrease in intima/media thickness have been described [46–49]. A meta-analysis of eight studies [46, 50–56] investigating the effect of Lp-apheresis in combination with drug treatment on coronary angiographic alterations demonstrated a trend-wise reduction of progression of CHD as compared to a group of patients treated by drugs only [32].

Due to the low prevalence of homozygous FH only few monitoring studies with hard cardiovascular endpoints are available. There are three recent publications in the literature available with a total of 95 patients with homozygous FH, 64 of them having been treated by regular Lp-apheresis [57–59]. In the majority the therapy was started at an age between 7 and 9 years. In about half of the patients atherosclerotic vascular lesions in particular at the aortic root and the coronary arteries were present already before the initiation of treatment. Despite an LDL reduction of 45–55 %, 20–35 % of the patients developed new lesions or showed progression of atherosclerosis during Lp-apheresis. Before introduction of Lp-apheresis homozygous FH patients rarely (< 20 %) survived the second decade. Clinical observations show an apparent increase in life expectancy as an indirect indicator for the efficacy of this type of treatment [28].

In 43 patients with heterozygous FH a 70 % reduction of coronary events due to Lp-apheresis treatment in combination with lipid lowering drugs as compared to 87 treated by drugs only has been seen [60]. This nonrandomized study with a small number of patients, however, did not show a difference concerning cardiovascular mortality. In a retrospective cohort study performed in Germany a reduction of cardiovascular events during Lp-apheresis-treatment (1.2 %/year) as compared to the one before initiation of treatment (7.0 %/year) has been described. In parallel a significant drop in the rate of revascularizations from 23.0 to 3.8 %/year was reported [61].

Another longitudinal cohort study in 120 patients with elevated Lp(a) (≥ 96 mg/dl before Lp-apheresis) and documented coronary atherosclerosis (angiographically > 50 % coronary artery stenosis and/or history of myocardial infarction) showed a significant Lp(a)-reduction (on average 73 %) in response to Lp-apheresis. This was

Table 3 Non-lipid effects of Lp-apheresis

Platelet activation ⇓
Markers of oxidative stress ⇓
Plasma- and whole blood viscosity ⇓
Mikroalbuminuria ⇓
Adhesion molecules ⇓
Inflammation (c-reactive Protein (CRP)) ⇓
Endothelial mediators (Nitric Oxide (NO), Prostaglandine I_2 (PGI_2)) ⇑

associated with an impressive 86 % reduction of clinical events [62]. Annual cardiovascular event rate of 1.056/patient under drug-treatment alone was lowered to 0.144/patient after initiation of Lp-apheresis.

c. Necessary monitoring

Before Lp-apheresis as well as regularly during the treatment, an evaluation concerning the presence, appearance or progression of atherosclerotic lesions is necessary (Table 4).

Table 4 Cardiovascular investigations during Lp-apheresis

Investigation	Before apheresis	Interval[a]
Vascular status	x	2 years
Sonography of abdominal aorta	x	Upon request
Carotid Sonography, intima-media thickness	x	2 years
Echocardiography	x	2 years
Non-invasive cardiac tests (scintigraphy, coronary CT)	x	2 years
Coronary angiography	x	Upon request

CT computed tomography
[a]with normal pre-value; in case of a positive result an individually closer monitoring is necessary

d. Evidence

As due to the introduction of Lp-apheresis, the life expectancy of homozygous FH patients has dramatically increased, there is a consensus of international societies nowadays that randomized studies are ethically unacceptable. The treatment has to be provided to all affected patients [63]. Also in the evaluation by the American Society for Apheresis (ASFA) LP-apheresis for homozygous FH shows the highest evidence level [64] and a strong recommendation according to grade (1a).

In heterozygous FH the evidence level is lower in category 2 as judged by the ASFA; meaning that Lp-apheresis is accepted as second line treatment after failing or insufficient response to other therapeutic (lifestyle modification, drug treatment) measures. For these patients a strong recommendation (grade 1a) is given. A similar level of evidence exists in patients with isolated elevated Lp(a). ASFA also categorizes in this indication the treatment into class 2, the grade of recommendation is 1b. Concerning the lack of randomized studies in this indication, it has to be mentioned that such a study was planned a couple of years ago in Germany [65], the protocol, however, has been rejected by the ethics committee due to positive results from cohort studies.

Methodology

a. Vascular access

Usually two peripheral arm veins are punctured. According to the veno-venous principle blood is drawn from a forearm vein; by means of a blood pump the cleaned blood will be reinfused via a second needle preferably on the contralateral arm. In case that a puncture on the contralateral arm is impossible, both venous accesses should be positioned at least in different flow paths of one arm. Due to the thrombophilia usually associated with hyperlipidemia in these patients, arterio–venous shunts are avoided as they frequently show early occlusion. Furthermore, in patients with cardiac insufficiency the high shunt volume may contribute to an impairment of cardiac function and symptoms.

b. Therapeutic systems

History

In the seventies of the last century for the first time methods for the treatment of homozygous FH by means of plasma exchange have been described [66]. Thereafter, several different methods of therapeutic haemapheresis have been developed, allowing a selective removal of apoB-containing lipoproteins such as LDL-C and Lp(a) in order to avoid the disadvantage of plasma exchange. Several procedures have been developed during the past. Today the earlier performed cascade filtration is mediocre and thus obsolete.

Immune adsorption

Human plasma is passing through columns covered with sheep antibodies against human apoB [67]. The binding of the apoB antibodies with the apoB-containing lipoproteins is soluble at acid pH by glycin, allowing the columns to regenerate and to be recovered several times during one treatment. The columns can be reused >70 times in contrast to the single use systems.

Dextrane sulphate adsorption

Cellular and plasmatic components of whole blood earlier were separated by a plasma filter. Today a whole blood system is in use. The plasma/blood rinses over dextrane sulphate on a cellulose matrix, which selectively binds

LDL-particles and Lp(a) due to the electrostatic properties [68]. The adsorption-columns are for single use only.

Heparin-induced extracorporeal LDL-precipitation (HELP)

This method is based on the principle that heparin precipitates LDL-C and Lp(a) in plasma if the pH is lowered (pH 5.1–5.2) [69]. The insoluble heparin-lipoprotein-complexes are removed by filtration. Subsequent bicarbonate dialysis normalizes subsequently the acid pH. As a consequence of this method, fibrinogen and other substances will precipitate. Therefore, the loss of fibrinogen limits the amount of plasma that can be treated per therapeutic session. Lowering of fibrinogen, which can also be observed using other principles, but to a lower extent, is discussed as an additive haemorheological advantage [41]. This could compensate the less pronounced LDL-C as well as Lp(a) lowering in part.

Direct adsorption of lipoproteins (DALI)

Using this whole blood system no plasma separation is necessary. Due to an electrostatic interaction of the lipoproteins with the polyacrylamide of the single use adsorber. LDL-C and Lp(a) are eliminated [70].

c. Anticoagulation

Depending on the antithrombotic therapy of the patient (i.e. oral anticoagulation, platelet aggregation inhibitors) as well as on the apheresis system application of additional anticoagulation can be considered. The DALI-apheresis system as well as the immune adsorption are using an ACD-A solution (acid citrate dextrose-A) anticoagulation, which is administered into the afferent tube-system, the rate is 1:20–1:40 relative to the blood flow.

d. Plasma volume and duration of treatment

During a therapeutic session using a flow rate of about 100–130 ml/min 6000 ml plasma are desorbed, the volume correlating asymptotically with the lowering of the lipoproteins. Using whole blood systems up to 10,000 ml of blood are treated. The duration of Lp-apheresis depends on the flow rate and the exchanged volume, it ranges between about 2.5 h using DALI-apheresis system and about 3.5 h using the immune adsorption. At the end of Lp-apheresis puncture sites are bandaged with compression bandings at least for a few hours up to the next day morning depending on bleeding tendency of the individual patients.

e. Patient care

Any apheresis treatment has to be performed in the presence of a medical doctor (iuspracticandi, specialist) as well as a certified medically trained assistant. Main aspects are the preparation of the Lp-apheresis machine, the monitoring during the therapeutic session as well as patient care. It must be warranted that alarms of the Lp-apheresis machine or any medical problem can be addressed immediately. An extensive teaching of the staff documented in written form for the respective apheresis system is required. Each therapeutic session has to be documented by a protocol.

f. Skipping of regular Lp-apheresis sessions

Surgical interventions, pneumonia or severe influenza and other severe diseases may require an interruption of Lp-apheresis therapy for a period of 2–3 weeks. During a short skipping of therapeutic sessions no rapid increase of lipoproteins occurs, the pre-values are not exceeded.

g. Side effects

Unwanted side effects during Lp-apheresis are relatively rare, mostly mild and usually easy to control. Local symptoms at the site of venous puncture are by far dominating, further temporary hypotension, muscular cramps and fatigue are claimed the most frequent side effects [72, 73].

The use of ACD-A as anticoagulant during treatment using whole blood systems is associated with the reinfusion of citrate-containing blood, which may result in hypocalcemia [71]. Infrequent symptoms of mild hypocalcemia such as paraesthesia, perioral twitch and muscle cramps can be avoided by oral calcium supplementation (fizzy tablets). In case the oral calcium supplementation is not done in time, or the reactions are already severe, an intravenous calcium substitution via a perfusor is necessary. The symptoms of hypocalcemia are intra-individually constant with high inter-individual variation, i.e. one single patient exhibits similar symptoms after a certain exchanged blood volume, between the patients there are, however, great differences.

The most severe side effect is an anaphylactic reaction described in patients who were taking ACE-inhibitors and have been treated with certain whole blood apheresis systems. The underlying reason is an activation of kallikrein–kinine-system with an associated decreased degradation of bradykinin as a consequence of kininase II inhibition due to the ACE-inhibitor therapy [74–77]. Therefore, ingestion of ACE-inhibitors during whole blood Lp-apheresis with DALI or dextrane sulphate adsorption is an absolute contraindication. Patients have to be informed about that before the initiation of treatment. A respective note should be mentioned in the obligatory written informed consent. Angiotensin-II-receptor blockers are not associated with this type of side effect and can be used safely as an alternative family of drugs [78]. Furthermore, ACE-inhibitors should also be avoided or at least used with caution during Lp-apheresis with immune adsorption

Centres in Austria

At present Lp-apheresis treatment is performed at the following centers in Austria:

Kärnten
Ambulatorium Ferlitsch, Spittal an der Drau (Dr. A. Ferlitsch)

Oberösterreich
Konventhospital of Barmherzigen Brüder Linz, Dept. of Internal Medicine (Prim. Univ. Prof. Dr. K. Lenz)
KH der Elisabethinen Linz, Internal Medicine 3 (N.N.)

Salzburg
LKH Salzburg, Dept. of Internal Medicine I (Univ. Doz. Dr. B. Paulweber)

Tirol
Medical University of Innsbruck, Dept. of Internal Medicine IV (Univ. Prof. Dr. G. Mayer)

Voralberg
Adults: LKH Feldkirch, Dept. of Nephrology and Dialysis (Prim. Univ.-Doz. Dr. K. Lhotta)
Children: LKH Feldkirch, Dept. of Pediatrics (Prim. Prof. Dr. B. Simma)

Wien
AKH Wien, Station 13I2 (Univ. Prof. Dr. K. Derfler)
Institute Athos (Univ. Prof. Dr. H. Sinzinger)

Summary

Lp-apheresis is a safe and effective therapy for patients with homozygous or therapy-refractory heterozygous familial hyperlipidemia, elevated Lp(a), intolerance against all lipid lowering agents and progression of atherosclerosis. The available various therapeutic principles are achieving a comparable lowering of LDL-C and Lp(a). An intensive multidisciplinary care for the patients including regular monitoring has to be performed in specialized centres.

Conflict of interest K. Derfler, S. Steiner, H. Sinzinger are heading a Lp-apheresis unit or are working at such a unit. All authors declare that there is no conflict of interest.

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