АФЕРЕЗ ЛИПОПРОТЕИДОВ: ВЧЕРА, СЕГОДНЯ, ЗАВТРА

Julius U., Tselmin S., Bornstein S. R.

Первые попытки лечения семейной гомозиготной гиперхолестеринемии (ГХ) плазмаферезом предпринимались в 60-70-е годы. Впоследствии, с появлением более специфичного метода — афереза липопротеинов (АЛ), отпала необходимость в замещении плазмы чужеродным белком. Была продемонстрирована решающая роль АЛ в продлении жизни этих больных, в то время как медикаментозная терапия показала в этих случаях значительно меньшую эффективность по сравнению с результатами её применения для лечения больных с другими типами ГХ. Тяжелые формы ГХ были признаны показаниями к применению АЛ у больных с сердечно-сосудистыми осложнениями. Повышенный уровень липопротеина(а) (Лп(а)) является международно признанным независимым атерогенным фактором риска. В связи с этим, экстракорпоральная терапия всё чаще проводится больным с повышенным Лп(а), страдающим такими тяжёлыми сердечно-сосудистыми осложнениями, как инфаркт миокарда или инсульт. В обзоре также обсуждается роль производимых в России колонок Лп(а) Липокак® (ЗАО НПФ "ПОКАРД", Россия) для специфического снижения липопротеина(а) в общем спектре методов АЛ. Ещё одним методом лечения станет в будущем антисмысловой олигонуклеотид для подавления синтеза аполипопротеина(а).

Российский кардиологический журнал. 2018;23(8):74–78
http://dx.doi.org/10.15829/1560-4071-2018-8-74-78

Ключевые слова: аферез липопротеидов, холестерин ЛНП, ЛНП аферез, липопротеид(а), антисмысловой олигонуклеотид для подавления синтеза апобелка(а).

Конфликт интересов: Julius U. получает гонорары от фирм Aegerion, Amgen, Chiesi, Sanofi, Kaneka, Diamed, Fresenius Medical Care, MSD, Tselmin S. получает гонорары от фирм Amgen, Sanofi, Fresenius Medical Care, Bornstein S. R. заявляет об отсутствии конфликта интересов.

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LA — lipoprotein apheresis, HCH — hypercholesterolemia, Lp(a) — Lipoprotein(a), CVD — cardiovascular diseases, LDL — low-density lipoproteins, PCSK9 — proprotein convertase subtilisin/kexin type 9, LDL-C — LDL cholesterol, TG — triglycerides, CVE — cardiovascular events.

Рукопись получена 08.06.2018
Рецензия получена 22.06.2018
Принята к публикации 04.07.2018

LIPOPROTEIN APHERESIS: YESTERDAY, TODAY, TOMORROW

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First attempts to treat patients with homozygous familial hypercholesterolemia (HCH) were performed in the 60s and 70s using a total plasma exchange. Later on, more selective lipoprotein apheresis (LA) methods have been developed — the replacement with foreign proteins was no longer necessary. It could be demonstrated that LA is life-saving in these patients, lipid-lowering drugs were shown to be much less effective than in other HCH patients. A severe HCH became an accepted indication for LA when cardiovascular events appeared. An elevation of Lipoprotein(a) (Lp(a)) is an internationally accepted independent atherogenic risk factor. Thus, an increasing number of patients with high Lp(a) concentrations suffering from life-threatening cardiovascular events like myocardial infarction or stroke started to be treated extracorporeally. Russian specific POCARD LLC "Lp(a) Lipopak®" columns are produced, their position within the LA methods is discussed. In the future, an antisense oligonucleotide against apolipoprotein(a) will represent another therapeutic option.

Russ J Cardiol. 2018;23(8):74–78
http://dx.doi.org/10.15829/1560-4071-2018-8-74-78

Key words: lipoprotein apheresis, LDL-cholesterol, LDL apheresis, lipoprotein(a), antisense oligonucleotide against apolipoprotein(a).

Conflicts of Interest: Julius U. gets fee from Aegerion, Amgen, Chiesi, Sanofi, Kaneka, Diamed, Fresenius Medical Care, MSD, Tselmin S. gets fee from Amgen, Sanofi, Fresenius Medical Care, Bornstein S. R. has nothing to declare.

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Introduction

In a previous publication the first author described the history of research in atherosclerosis, of the introduction of lipid-lowering drugs and of lipoprotein apheresis (LA) into medical practice [1]. This current review focuses on recent tendencies and is based on the rich experience of all authors with LA at the Dresden Center for Lipoprotein Apheresis, where at present more than 130 patients are treated. We are the only center worldwide where 6 different LA methods are used. We published data showing the effectiveness of these methods and differences between them [2, 3].

Lipid disorders as atherogenic risk factors

Lipid disorders are often seen in a population and represent severe risk factor to develop atherosclerotic lesions [4]. The latter can lead to cardiovascular diseases (CVD) like myocardial infarction, peripheral arterial occlusive disease, occlusion of the carotids, stroke, atherosclerotic plaques at the aorta, stenosis of the aortic valve.

Both genetic and life-style factors underlie these lipid disorders. When genetic factors dominate several family members are affected. Two lipoproteins play a major role: low-density lipoproteins (LDL) and Lipoprotein(a) (Lp(a)).

Familial hypercholesterolemia (HCH) is caused by mutations of the LDL receptor gene (more than 1700 mutations are known), of the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene, and of the apolipoprotein B gene.

Patients with a homozygous familial HCH — both alleles of the LDL receptor gene have mutations — are characterized by especially severe and early (beginning in the childhood) atherosclerotic lesions [5]. Their life expectancy is rather limited — usually these patients die at the age of less than 20 years when not effectively treated. Among patients suffering from a myocardial infarction a heterozygous familial HCH is an important atherogenic risk factor. A combined hyperlipidemia exhibiting both an elevation of LDL cholesterol (LDL-C) and of triglycerides (TG) is also inducing CVD [6].

Lp(a) had been detected in the early 60ies. Several epidemiological studies showed its significance as an independent atherogenic risk factor [7-9]. This fact has been proven in studies using the Mendelian randomization approach and in studies looking into mutations of the Lp(a) gene [10].

LA yesterday

In the 60ies, the urgent need to effectively treat patients with homozygous familial HCH was recognized and a total plasma exchange was started in France and Great Britain [11, 12].

In these years, no drugs were available to reduce the extremely elevated LDL-C concentrations, and patients usually died at an early age. In the 70ies and the 80ies different lipoprotein apheresis methods were developed in Japan, in Russia and in the Federal Republic of Germany [1]. Usually, an LA therapy was started within secondary prevention. But in children suffering from homozygous familial HCH the extracorporeal treatment should be started early before atherosclerosis develops.

The first author of this minireview got his first experience with Russian and Japanese LA methods at the Apheresis Unit of the USSR Cardiology Research Center of the Academy of Medical Sciences in Moscow in 1987 (Head: Prof. V. V. Kukharchuk). In these years, the number of patients treated extracorporeally was everywhere rather low. The majority of them suffered from homozygous familial HCH or from severe HCH associated with life-threatening CVD.

At the Lipidological Center in Dresden we treated whole families whose members were affected from familial HCH. We saw several of them dying. That is why scientists at the Institute of Clinical Chemistry and Laboratory Medicine at the Medical Academy Dresden produced LA columns which were never used due to the fact that no plasma filters were available (they would have to be imported from Western countries). Thus, in Dresden we started to treat patients with LA only in 1990 after the German reunification.

Statins became available on a large scale in the 90ies [1]. They were effective with respect to lowering LDL-C levels, to decreasing cardiovascular morbidity and mortality. But in spite of taking a statin, some patients develop cardiovascular events (CVE) for several reasons: 1. target values were not reached, especially with statins of lower potency or when a severe mutation of the LDL-receptor gene was present, 2. statins were not well tolerated by some patients, 3. other risk factors like a diabetes mellitus or a chronic renal insufficiency played a role. For these patients an LA was a therapeutic option. And in the late 90ies, a study in patients with heterozygous familial HCH showed the efficiency of the extracorporeal therapy with respect to CVE rates when comparing with a statin therapy alone [13]. Case reports from several groups confirmed this effect [14, 15].

After 2000, Lp(a) was more and more recognized as an independent atherogenic risk factor [16]. Lipidologists, cardiologists and angiologists measured this parameter especially in patients who had multiple CVE though their LDL-C concentrations were not very high. In Germany, the Joint Federal Committee accepted an isolated elevation of Lp(a) as an indication for LA in 2008. In 2009, a retrospective study was published showing the high effectiveness of an LA treatment on CVE rates in these patients [17]. These findings could be confirmed in a prospective study in 2013 and 2016 [18, 19]. We had shown that the reduction of CVE when comparing the situation during LA therapy with that before the start of an LA therapy was much higher in patients exhibiting an elevation of Lp(a) and not only a HCH [20, 21].

Since the early 90ies, in Moscow the specific POCARD's "Lp(a) Lipopak" columns have been produced which exclusively decrease Lp(a) and not LDL-C (as all other LA methods do) [22]. In a study, published in 2013, with coronary angiography before the start of this specific Lp(a) apheresis and after 18 months, a positive effect of the extracorporeal therapy on coronary atherosclerosis could be shown [23].

LA today

LA is performed in several countries, but the differences in numbers of patients are striking. Of course, LA is an expensive and laborious therapy but the benefit for the patients is immense. Economic reasons do not fully explain the differences between countries. Even in some rather rich countries LA is hardly being used. A major problem is the attitude of the medical community to LA — LA is often not known among cardiologists and nephrologists. Some critics say that the medical care which is offered to patients on LA sessions (including a psychological support by the medical staff, regular visits by a physician who cares for all risk factors in a given patient) is more important for the fate of the patients than the extracorporeal procedure itself.

Even in Germany, where a homozygous familial HCH, a severe HCH and an isolated elevation of Lp(a) are

Table 1

Official indications for LA in Germany [2]

• 1. homozygous familial HCH,
• 2. severe hypercholesterolemia, if the maximal documented diet and drug therapy for more than one year failed to lower LDL-C sufficiently,
• 3. elevation of Lp(a)) levels ⩾600mg/L (⩾120nmol/L) and (clinically or by imaging technique) documented progressive cardiovascular diseases.

officially reimbursed by the health insurance companies (Table 1), only a small percentage of patients with an indication for LA therapy is in fact treated with LA.

Usually, an LA is performed when CVE had occurred. The only exception to this rule is young patients with a homozygous familial HCH who should be treated already in the childhood. In these patients, statins are much less effective than in other patients. Even PCSK9 inhibitors show a rather low effectiveness (LDL-C is reduced by about 30% provided the LDL receptor function is still present; when no LDL receptor function has been left PCSK9 inhibitors are totally ineffective). Usually LA sessions do not guarantee reaching the LDL-C target level (below 2,6 mmol/l or even below 1,8 mmol/l), thus in individual cases more than one session per week are required. An additional possibility to essentially lower the LDL-C concentration would be to prescribe the microsomal transport protein inhibitor lomitapide for these patients [5]. It had been reported that in some patients this drug allowed to stop the LA therapy [24]. Though adverse effects like a steatosis hepatis and gastrointestinal complaints are a major concern [25].

According to the officially published data, in Germany about 100 patients with homozygous HCH have been treated with LA in 2016 [26].

Recently, the indication for an LA in patients with severe HCH (heterozygous familial HCH or polygenetic HCH) has been seen more restrictively. The number of patients reaching LDL-C target values (<1,8 mmol/l in high-risk patients) has increased for 3 reasons: 1. more potent statins (atorvastatin, rosuvastatin) are used more often, 2. ezetimibe is administered in an increasing number of patients in addition to a statin, 3. since 2015 PCSK9 inhibitors are injected more often, especially in patients with a statin-intolerance. Thus, an LA treatment in patients with severe HCH should be started when the CVD are critical or have progressed and the target value for LDL-C could not be reached (e.g. when all lipid-lowering drugs are not tolerated). At least in Germany, the apheresis committees of the Associations of Statutory Health Care Physicians (which should confirm the applications for a given patient to start LA therapy) usually demand that PCSK9 inhibitors should be given before beginning an extracorporeal therapy. In patients on LA therapy, additional injections of a PCSK9 inhibitor may be performed when the pre-LA session LDL-C levels remain high and new CVE occurred.

In Germany, the number of patients being treated with LA with the diagnosis "severe HCH" amounted to 1700 in 2016 [26]. At the Dresden Center for Extracorporeal Treatment, no new patient started an LA with this diagnosis in 2017.

On the other hand, the number of patients beginning an extracorporeal therapy with the indication "isolated elevation of Lp(a)" steadily increased during the last years and according to the official German data was equal to 1468 patients in 2016 [26]. In our own experience, some patients exhibit both an elevation of LDL-C (though taking lipid-lowering drugs when tolerated) and of Lp(a) — these patients are not reported separately in the official documents.

It has to be stressed that at present no drug therapy to reduce Lp(a) levels is available. Nicotinic acid had been withdrawn from the market due to inefficiency with respect to outcome data [27].

Patients who got the permission for LA with the indication "isolated elevation of Lp(a) are typically characterized by one or several of the following situations: 1. CVE occurred at a rather young age (before 50 years), 2. patients needed multiple interventions, e.g. at the coronary or leg arteries, 3. several vascular territories are affected (carotids, coronary and leg arteries, aorta), 4. patients have a positive family history with CVE in first-degree relatives before the age of 60 years. In a few patients new CVE were seen, even when patients came regularly to the LA center. We treated these patients successfully with two sessions per week.

A single-blinded randomized controlled trial was conducted in 20 patients with refractory angina and raised Lp(a) >50 mg/dl, with 3 months of blinded weekly LA or sham, followed by crossover after a 4 weeks interval between the extracorporeal procedures [28]. The true LA sessions increased myocardial perfusion, improvements with apheresis compared with sham also occurred in atherosclerotic burden as assessed by total carotid wall volume (assessed by MRT), exercise capacity by the 6 min walk test, 4 of 5 domains of the Seattle angina questionnaire and quality of life physical component summary by the short form 36 survey (SF-36).

The specific POCARD's "Lp(a) Lipopak" columns should be preferably used in patients whose LDL-C is rather low on the background of an effective lipid-lowering drug therapy. More outcome data with these columns are needed.

LA tomorrow

There is no doubt that a total plasma exchange should not be applied any longer in the long run to treat patients with lipid disorders, but it may be performed in patients with a chylomicronemia syndrome who suffer from an acute pancreatitis — only one to two sessions are needed.

Due to the extremely high atherosclerotic risk and the reduced or absent efficiency of lipid-lowering drugs,

patients with a homozygous familial HCH will survive only with the help of an LA therapy. This indication is internationally accepted [29].

There will be a competition between LA and new lipid-lowering drugs, like PCSK9 inhibitors, therapeutic RNA interference (RNAi) inhibitor of PCSK9 [30]. It has to be taken into consideration that LA exerts also pleiotropic effects which most probably have an additional positive effect on the patients [2]. Most of these pleiotropic effects have not been observed with modern drugs. Prospective studies comparing outcome data for LA and modern drugs should be planned. But there will always remain some patients with a severe HCH in whom drugs are not tolerated or who cannot reach LDL-C target levels. Of course, an LA will always be the last therapeutic step, it should be performed in addition to lipid-lowering drugs when tolerated.

For patients with extremely high Lp(a) concentrations, it has still to be demonstrated whether the current strategy to maximally lower LDL-C will be optimal with respect to CVE or whether the additional reduction of Lp(a) is necessary. Probably this question will be answered in part when further analyses of the big PCSK9 inhibitor outcome studies will be published (Fourier, Odyssey Outcome).

The role of the specific POCARD's "Lp(a) Lipopak" columns has still to be better defined. Very low LDL-C levels, which could be avoided by using these columns, do not seem to induce adverse effects in the PCSK9 inhibitor studies (Fourier, Odyssey Outcome).

On the horizon, there is a new antisense oligonucleotide against apolipoprotein(a), which can reduce Lp(a) concentrations up to 90% [10, 31]. Phase III studies will soon start. But the authorities will require to have a look at outcome data before it will be officially registered. Surely, the drug will be rather expensive.

In Germany, an LA registry was started [32]. It would be optimal to include all patients who are treated world-wide in such a registry — in order to offer the option to demonstrate the effectiveness of LA on CVE in a big population and to compare different LA methods with respect to outcome data.

Surely, nobody should be afraid of adverse effects of LA — they are no major problem in experienced LA centers [33].

Conclusions

CVD are a major reason for morbidity and mortality. Attention to atherogenic risk factors should be increased. Specialists in lipidology are needed, nephrologists should start LA therapy. At least in developed countries an active therapeutic approach must be exercised including all possibilities of modern medicine with the aim to save costs for cardiovascular interventions — the number needed to treat (NNT) in the Pro(a)Life study was 3.

A regular (optimal: weekly) LA therapy can only be offered to patients who are highly compliant with respect to an optimal life style (no smoking, healthy nutrition, physical activities) and to intake of prescribed drugs. The extracorporeal therapy should be performed life-long. It can be stopped when a malignant tumor was detected, the general condition of the patient has worsened, a patient is no longer able to walk. Contraindications to LA have to be taken into account.

It will be necessary to diagnose a homozygous familial HCH already at a very young age. Relatives of patients who suffered from CVE should be screened for LDL-C and Lp(a) and should be treated appropriately. The relevance of elevated Lp(a) should be recognized to a much greater extent by specialists.

Conflicts of Interest: Julius U. gets fee from Aegerion, Amgen, Chiesi, Sanofi, Kaneka, Diamed, Fresenius Medical Care, MSD, Tselmin S. gets fee from Amgen, Sanofi, Fresenius Medical Care, Bornstein S. R. not declared.

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