

Improvement of radiocephalic fistula maturation: rationale and design of the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study – a randomized controlled trial

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ABSTRACT

Background: Non-maturation is a frequent complication of radiocephalic arteriovenous fistulas (RCAVF). In an animal model, liposomal prednisolone improved maturation of experimental fistulas. The Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study investigates if liposomal prednisolone improves RCAVF maturation.

Methods and results: The LIPMAT study is an investigator-initiated, multicenter, double-blinded, placebo-controlled randomized controlled trial with 1:1 randomization to liposomal prednisolone or placebo. Eighty patients receiving an RCAVF will be included. The primary outcome is the cephalic vein diameter six weeks after surgery, measured by ultrasound. The LIPMAT study started in May 2016. Enrollment is expected to be completed by the end of 2017.

Conclusions: The LIPMAT study is the first to evaluate the efficacy of liposomal prednisolone to enhance RCAVF maturation.

Keywords: Liposomal prednisolone, Maturation failure, Nonmaturation, Radiocephalic AVF

Introduction

AVF maturation

Maintenance hemodialysis patients require a reliable vascular access. The autologous arteriovenous fistula (AVF) is the

preferred type of vascular access, with superior long-term patency rates and lower infection rates compared to arteriovenous grafts (AVGs) and central venous catheters (CVCs). The suitability of an AVF for hemodialysis depends on its diameter, blood flow, depth and usable length (1, 2). Patients requiring hemodialysis while their AVF has not matured may be exposed to the risks and burden of CVC use, angioplasty procedures and surgical reconstructions.

Upon AVF creation, the vein is exposed to arterial blood pressure and a high blood flow, increasing wall shear stress and wall tension. The vein adapts favorably by outward remodeling, increasing luminal dimensions, and unfavorably by intimal hyperplasia, decreasing luminal dimensions (3).

Maturation of AVFs can be disrupted by arterial abnormalities, pre-existing venous damage, surgical failure or a mismatch between outward remodeling and intimal hyperplasia. Non-maturation of AVF occurs frequently, as illustrated by the results from a large clinical trial by Dember et al (4) in which 60% of AVFs did not meet suitability criteria. Non-maturation

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was higher (64%) for radiocephalic AVFs (RCAVF) when compared to upper-arm AVFs (53%).

Improvement of maturation by liposomal prednisolone

In preclinical studies in pigs (5) and mice (6), significant vascular inflammation was observed in the vein near the arteriovenous anastomosis early after AVF creation. This most likely relates to injury by surgical manipulation or blood flow and shear stress far beyond values normally found in veins. This transient inflammation was hypothesized to inhibit maturation by initiating migration of vascular smooth muscle cells and myofibroblasts and limiting outward remodeling, thereby promoting the formation of stenosis (5). In an observational human study, elevated inflammatory markers were indeed associated with AVF non-maturation (7). We hypothesized that inhibiting this inflammation may improve AVF maturation.

Glucocorticoids (GCs) are potent inhibitors of inflammation, although the therapeutic use of systemic GCs is hampered by various adverse side effects on non-target tissues (8). Nanoparticle therapeutics such as liposomes have been shown to facilitate selective delivery of drugs to inflamed tissues, thereby limiting systemic side effects (9). PEG-liposomal prednisolone sodium phosphate (Nanocort®, Enceladus Pharmaceuticals B.V., Naarden, The Netherlands) consists of lipid vesicles encapsulating prednisolone, a potent glucocorticoid. The intact endothelial lining is poorly permeable to circulating liposomal prednisolone. Together with low degradation in the reticuloendothelial system, this results in a plasma half-life of around three days and therapeutic efficacy of two weeks after a single intravenous infusion. The leaky endothelium at sites of inflammation is permeable to liposomes, resulting in high concentrations of liposomal prednisolone in target tissues (10). This results in a strong therapeutic effect with limited side effects. After successful pre-clinical proof of concept studies, the efficacy of liposomal prednisolone in active rheumatoid arthritis is under evaluation in a multicenter phase 3 study (EudraCT identifier: 2015-002924-17).

We selected liposomal prednisolone as the candidate drug to evaluate the hypothesis that inhibition of inflammation improves AVF maturation. In mice, two weeks after creation of a carotid-jugular AVF, liposomal prednisolone increased the juxta-anastomotic venous circumference by 27% ($p = 0.004$) and the luminal area by 47% ($p = 0.042$) when compared to saline (11). In contrast, free prednisolone and empty liposomes did not improve circumference or luminal area. No significant differences in intimal area were observed, indicating that the differences in luminal area are the result of improved outward remodeling rather than inhibited intimal hyperplasia.

Study design and treatment

The Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study (ClinicalTrials.gov identifier: NCT02495662) is a phase 2, investigator-initiated, multicenter, double-blinded, placebo-controlled randomized controlled trial evaluating the effect of liposomal prednisolone on the maturation of RCAVFs. Patients will be asked for

informed consent when referred for creation of an RCAVF, based on pre-operative vein mapping according to local care standards in each hospital. Exclusion criteria include an ipsilateral CVC, current malignancy, latent or active infections with tuberculosis or hepatitis B and C, uncontrolled diabetes mellitus and known contraindications to glucocorticoids. In addition, the use of systemic glucocorticoids, immunosuppressant medication or NSAIDs is not allowed.

The trial subjects will receive AVF surgery in their own hospitals, with surgical techniques and anesthesia according to local care standards. If an RCAVF has been successfully created, subjects are randomized 1:1 to liposomal prednisolone or placebo (Fig. 1). Subjects are treated twice: one day after surgery and two weeks thereafter to achieve a treatment effect lasting four weeks following surgery. At each treatment visit, 150 mg liposomal prednisolone in 500 mL normal saline is administered in the arm contralateral to the AVF, or 500 mL normal saline as a sham infusion. The patients, investigator and the patients' physicians are blinded to the group allocation. Blinding is achieved through a fully opaque IV set equipped with an air filter permeable to the 110 nm liposomes (IVSTAR-F 4.3cm² 1.2 μm pore size, CODAN GmbH, Lensahn, Germany) and an opaque cover around the infusion bag. Prior to each infusion, the AVF is evaluated for patency and wound complications by physical examination. If patency cannot be determined by palpation and auscultation, a duplex ultrasound is performed prior to treatment.

After AVF creation and study treatment, subjects receive follow-up in their own hospitals. Surgical, endovascular or drug treatments aimed to improve the AVF outcome are allowed and at the discretion of the patient's treating physician. Maturation of these AVFs is considered assisted.

Endpoints

The main study endpoint is the diameter of the cephalic vein at 1 cm downstream from the anastomosis, measured by duplex ultrasound 6 weeks after AVF creation. Secondary endpoints are the cephalic vein diameter at the elbow and mid upper arm and the blood flow in the cephalic vein, radial artery and brachial artery. As secondary endpoints, these measurements are repeated at 3 months after AVF creation. Ultrasound technicians in all participating hospitals perform these follow-up ultrasound measurements, according to the study protocol, in addition to any measurements normally performed in routine care. Occlusions of the AVF and procedures performed to improve AVF maturation are recorded as secondary endpoints.

Statistics

Sample size calculation

In a pilot analysis in our center, the mean distal cephalic vein diameter at six weeks after AVF creation was 5.4 mm with a standard deviation of 1.5 mm. A 20% improvement of the distal cephalic vein diameter was chosen as a clinically relevant treatment effect, corresponding with a 1.0 mm increase. The sample size of the LIPMAT study was chosen to detect this 1.0 mm difference between the study groups with a power of 80% at an alpha level of 5%. Based on these assumptions, 36 subjects per

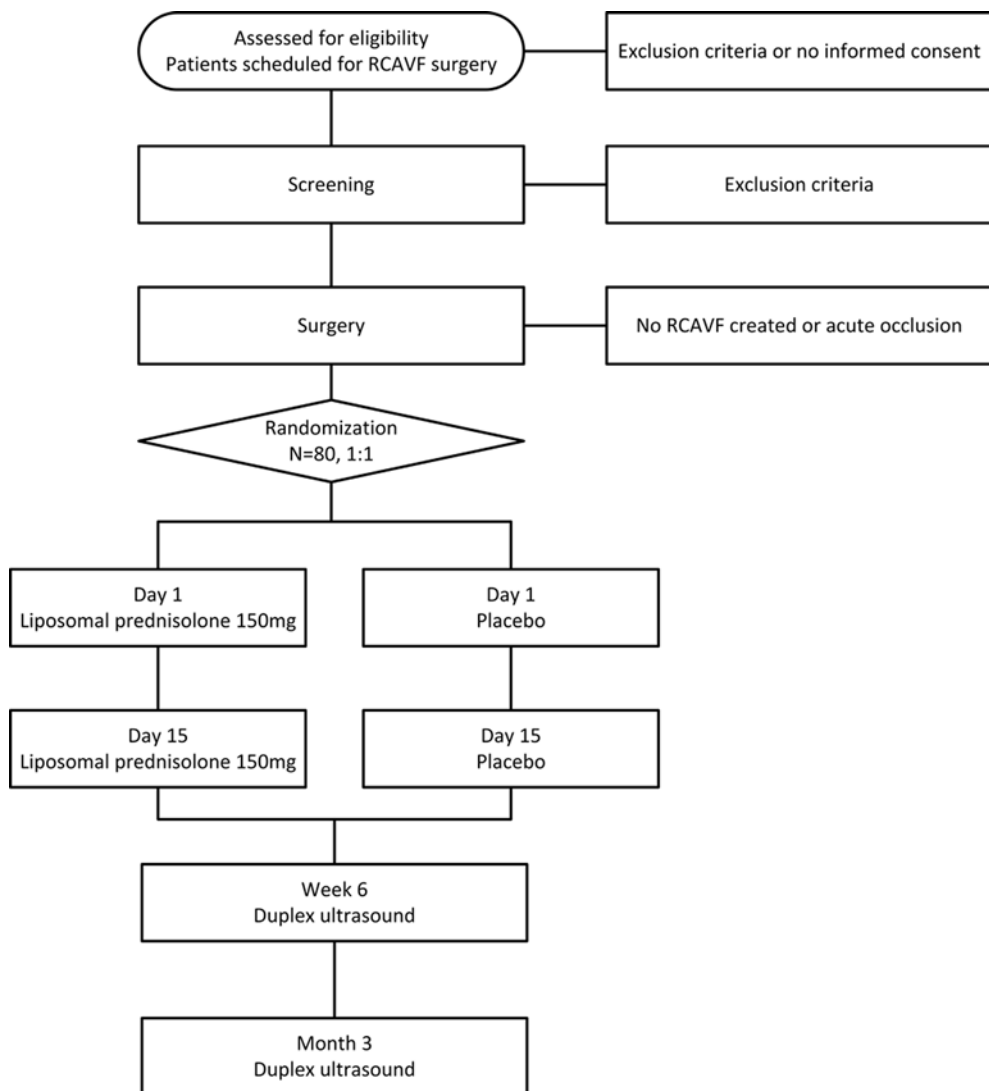


Fig. 1 - Flow chart of the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study.

group are required. Allowing for a 10% drop-out, 40 subjects per group will be included, for a total of 80 subjects.

Efficacy analysis

The primary and secondary endpoints will be reported descriptively as mean ± standard deviation. The means of the continuous variables in the primary endpoint will be compared between groups for statistically significant difference using the two independent sample *t*-tests. In case of non-normality, a non-parametric test will be used. The proportions of AVF occlusion and assisted maturation will be reported as percentages per treatment group.

Time line

The protocol was approved by the ethics committee in November 2015. The first patient was treated in the trial in May 2016. Currently, nine centers have agreed to participate in the LIPMAT study. As of November 2016, 15 subjects have provided informed consent for the study, of which 11 have re-

ceived the study treatment. Two subjects were not randomized because no RCAVF was created, one withdrew consent before AVF surgery and one was excluded for latent tuberculosis. Thirty-five more patients provided consent for screening, but were excluded for comorbidities or prohibited concomitant medication.

Discussion

Non-maturation of RCAVFs is the most important limitation of this type of vascular access. The LIPMAT study is one of the few current randomized controlled trials aimed at improving AVF maturation with a novel pharmacological intervention.

Choice of endpoints

In this phase 2 study, our goal is to evaluate whether medical treatment improves maturation of RCAVFs. As a continuous endpoint provides greater power with a feasible sample size, the cephalic vein diameter at a standardized location



was chosen, rather than criteria for maturation by The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) (1) or Robbin et al (2). Since the majority of patients who receive an RCAVF in our region have not yet initiated hemodialysis, successful cannulation is not a feasible endpoint in the current study as this would significantly prolong follow-up. We aim to evaluate long-term functional outcomes in a follow-up study.

Timing of study procedures

In practice, surgeons may decide to create another type of vascular access if vessels are smaller than expected. As no measurement of endpoint is possible in these subjects, they are not included in the study. Although subjects are screened before the planned RCAVF surgery, actual inclusion and randomization is performed only if an RCAVF was successfully created.

The timing of the first treatment one day after surgery was chosen to prevent treatment of subjects who cannot benefit from treatment and cannot provide endpoint measurements. By not treating preoperatively, subjects who unexpectedly receive another AVF configuration are not treated unnecessarily. In cases of early postoperative RCAVF thrombosis and no successful AVF salvage-interventions, subjects are not treated. Finally, as glucocorticoids are known to impair wound healing, the treatment at one day after surgery allows for inspection of the wound to exclude subjects with early wound complications and prevent treatment harm. Subjects are treated twice with a two-week interval to achieve four weeks of drug activity. As shown by Robbin et al (12), most of the diameter and flow increase during maturation occurs within this time frame.

Improvement of inclusion

The current rate of inclusion reflects the start-up phase of the study, with several centers starting inclusion recently. An additional factor could be the relatively high frequency of upper-arm AVFs in our region. Several patients have also been excluded for concomitant use of immunosuppressant medication. We aim to increase the rate of inclusion by further expanding the study to other hospitals within the Netherlands.

Conclusions

AVF non-maturation remains a challenge for nephrologists, vascular surgeons and dialysis patients. With promising results from preclinical experiments in AVF maturation and growing human experience with liposomal prednisolone, the

LIPMAT study is the first to investigate this novel drug for AVF maturation. The LIPMAT study started in May 2016 and the expected inclusion of the 80th subject will be late 2017.

Disclosures

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Conflict of interest: The authors declare no conflict of interest.

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