The haemodialysis arteriovenous graft: is a new era coming?

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Introduction

The worldwide increase in the incidence and prevalence of haemodialysis (HD) patients is determining the growing demand of vascular access (VA) placement [1]. It is also well-known that the VA issue imposes a major financial burden on healthcare systems and can be associated with increased morbidity and mortality [2]. VA dysfunction is a major cause of morbidity and mortality in HD patients [3]. Between the Fistula First Breakthrough Initiative [4] and strategies for decreasing the use of HD catheters, ‘fistula first/catheter last’ [5], there is a renewed research effort aimed at improving the poor outcomes of arteriovenous graft (AVG). In fact, the major disadvantages of synthetic AVGs include the development of graft stenosis, a 5-fold increase in infection risk, a poorer long-term patency, higher levels of complications and more interventions than autogenous arteriovenous fistulas (AVFs) [6]. At the present time, for nephrologists, AVG means reduced primary patency rates, hospitalizations, use of central vein catheters, invasive surgical or less invasive interventional procedures, increased morbidity and mortality beyond the aspect of increase in costs. In this issue of Nephrology Dialysis Transplantation, Paulson et al. [7] provide evidence that an easily clinically applicable therapy, such as the periadventitial delivery of sirolimus, may improve HD graft patency and prolong its functional life.

AVG stenosis: a compulsory route

The most common cause of VA dysfunction is stenosis. It occurs most commonly in AVG at the graft vein and juxta-anastomotic vein segment and is primarily due to venous neointimal hyperplasia. The surgical trauma at the time of AV surgery, haemodynamic shear stress at the vein graft anastomosis, graft bioincompatibility, vessel injury due to repeated cannulations, uraemia resulting in endothelial dysfunction and repeated angioplasties causing further endothelial injury are the factors that contribute to the neointimal hyperplasia [8]. We should also keep in mind that additional factors involved in neointimal hyperplasia and stenosis development are the surgical expertise, design of anastomosis (angle between graft and vein, length of anastomosis), use of ‘hooded’ expanded polytetrafluoroethylene (ePTFE) grafts, interindividually different circulatory and rheological conditions [9].

Histological and immunohistochemical analysis of stenotic segments have documented the presence of α-smooth muscle actin-positive cells, myofibroblasts and microvessels within the neointima, abundance of extracellular matrix components, angiogenesis (neovascularization) within the neointima and adventitia, a macrophage layer lining the perigraft region and an increased expression of mediators and inflammatory cytokines such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF) and endothelin within the media, neointima and adventitia [10, 11]. These cells express markers that characterize them as myofibroblasts and express vimentin and α-smooth muscle actin but not markers, such as desmin and smoothelin [12]. It is unknown whether these myofibroblasts are transformed fibroblasts migrating from the adventitia that develop a smooth muscle cell actin expression to become myofibroblasts or contractile smooth muscle cells migrating from the media which lose desmin expression and acquire vimentin expression. The new hypothesis is that the adventitial fibroblasts are transformed into myofibroblasts and begin to proliferate within hours after graft placement. Migration of these cells towards the vessel lumen with subsequent proliferation appears to be a major contributor to neointimal hyperplasia formation. Many of the described mechanisms result in an increase in the production of free radicals. Clinical studies of stenotic AVGs have demonstrated an up-regulation of metalloproteinases and have documented the colocalization of oxidative stress markers with inflammatory cytokines such as TGF-β and PDGF within neointima of stenotic AVGs [13]. The pivotal role of the adventitial fibroblasts provides a compelling rationale for therapies that target the transformation, proliferation and...
migration of these cells to prevent AVG stenosis [14]. More recently, data from experimental stenosis models have shown that smooth muscle cells in the neointima may also originate from bone marrow-derived cells that bind the site of vascular injury and later differentiate into a smooth muscle cell phenotype in the neointima [15].

**Novel therapies in AVG stenosis**

There have been few effective treatments to date for venous neointimal hyperplasia because of the poor understanding of the pathogenesis of venous neointimal hyperplasia. More recently, the knowledge of the pathogenesis of VA stenosis has provided a framework for development of therapies that target neointimal hyperplasia. The treatments to inhibit VA stenosis include (i) perivascular treatments (wraps, gel): delivering of a drug or vector or cells that inhibit cell proliferation and/or migration and/or promote dilation; (ii) localized surface treatments: target heat, cold, radiation, to induce cell apoptosis, promote dilation. The ultrasound exposure of an ePTFE graft can generate temperatures sufficient to prevent cell growth on the graft without damaging nearby soft tissues and blood. In a graft/tissue model, the ultrasound heating reduced neointimal hyperplasia and failure of ePTFE vascular grafts [16]; (iii) localized endovascular treatments (targeted treatments, not stents): delivery of drugs, protein, etc. that inhibit cell proliferation and/or migration: among local drug delivery systems for HD VA, there are also gel–foam wraps loaded with treated human aortic endothelial cells [17], vascular endothelial growth factor D gene therapy [18] and recombinant pancreatic elastase PRT 201 applied at the outflow vein at the time of surgery [19]. Furthermore, the endovascular radiation therapy has been proposed to treat vascular stenosis due to its anti-proliferative effects. A recent randomized controlled trial in 25 patients bearing AVGs has shown that 42% of radiated AVGs achieved the target lesion primary patency end point at 6 months as compared to 0% of the controls; however, this did not translate into an improvement in secondary patency rates [20].

**Perivascular treatments**

The rationale of perivascular treatments is that dialysis AVGs could be an ideal model for use of perivascular therapies since they can be applied at the time of surgery. The perivascular therapies target the adventitia and now, we know that lipophilic molecules when placed over the adventitia rapidly diffuse through all the layers of the vessel wall. The small amounts of toxic drugs can be safely delivered to the site of stenosis resulting in high local concentrations with minimal systemic toxicity [10]. Experimental *in vitro* studies have demonstrated the efficacy of sirolimus and paclitaxel eluted from stents on the inhibition of cell proliferation. Both sirolimus and paclitaxel inhibit smooth muscle and endothelial cell proliferation. However, the mechanism is different: sirolimus reduces neointimal hyperplasia through a cytostatic mechanism, while paclitaxel produces apoptotic cell death [21]. Animal studies have demonstrated the efficacy of paclitaxel-eluting wraps in AVG stenosis with anti-proliferative effects [22] and that sirolimus-loaded polyurethane grafts have improved patency rate and less neointimal hyperplasia, although the results were not statistically significant [23].

In 2007, a large multicentre randomized controlled trial, evaluating the use of paclitaxel-eluting mesh wraps, was initiated to study the effectiveness and safety of this therapy on primary AVG patency compared to a standard AVG. However, this study was suspended in 2009 following a data safety monitoring review due to an imbalance in the incidence of infections in one of the arms (either control or treatment). An alternative approach is the use of sirolimus-eluting COLL-R® wraps. An initial Phase II study demonstrated primary unassisted patency of 75 and 38%, respectively, at 1 and 2 years [24].

The study by Paulson *et al.* is the first in-human study that clearly demonstrates the technical success and safety of sirolimus-eluting COLL-R® wraps + graft combination in 12 patients. The patients received a PTFE AVG with a sirolimus-eluting collagen matrix wrapped around the graft venous anastomosis. Twelve- and 24-month primary unassisted patencies were, respectively, 76 and 38%; the secondary assisted patencies were, respectively, 84 and 52%. The thrombosis rate was at 0.37 per patient-year [7]. These results exceed that in previous studies which have ranged from 23 to 43% [25] with a thrombosis rate of 0.41–1.03 per patient-year [26]. Although the study lacks a control group to properly address patency and does not report the technical aspects, it demonstrates for the first time in dialysis AVG that periadventitially implanted Coll-R® wrap can safely deliver sirolimus and suppress neointimal hyperplasia.

Some critical issues about such a therapy must be underlined: although it is unlikely that the local delivery of the drug would result in systemic toxicity, a still critical issue in any delivery system is the need to match the temporal profile of drug release to the biological sequence of events that characterize the disease process [9]; furthermore, we do not know whether the initial prevention of neointimal hyperplasia will be able to prevent the late occurrence of graft stenosis; in addition, the cost issue may be a matter of concern. However, the most important critical issue is the need of long-term randomized control studies with three arms: autologous AVFs, conventional ePTFE AVGs and sirolimus-coated ePTFE AVGs.

In addition, there is a first clinical observation, published by Patané *et al.* [27] in 2009, about the use of a paclitaxel-coated balloon in VA stenoses. Further studies are needed.

Finally, a few words are needed about VA policy: our patients are long-term patients who expect, with good reason, a VA with a long-term functional perspective. The patients who would profit from the sirolimus-eluting wrap have an AVG. Thus, they represent a minority of the total patient population. Although we have convincing data about the superiority of autologous AVFs, we observe a worldwide increase in catheter use and a comparatively low AVF use [3–6]. Here, we assume, are the real challenges in the field of VA with a lot of unanswered questions.
Conclusions and future perspectives

VA stenosis is a pervasive problem in HD patients. The stenosis of AVGs may require chronic treatment and perivascular applications seem to be a logical approach. Whether this easily clinically applicable therapy may prolong the life and reduce the costs of AVGs awaits confirmation from long-term randomized control studies.

In order to advance the field further, we need to improve our current understanding of both the clinical and experimental pathways that result in venous neointimal hyperplasia by using the advanced technologies and tools in cellular and molecular biology, bioengineering, genomics, proteomics and vascular imaging. Finally, small and large animal models of AVG, which a number of investigators in this field have already developed, will play an essential role in translating our knowledge of pathophysiological mechanisms in VA dysfunction to novel therapies for patients [8].

Conflict of interest statement. None declared.


References

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