National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: May 2018

Refanalin for delayed graft function following kidney transplant

NIHRIO (HSRIC) ID: 11101 NICE ID: 9622

LAY SUMMARY

Delayed graft function (DGF) is a complication that can occur in a patient immediately after they have a kidney transplant, particularly if the organ donor was deceased. If a patient develops DGF they will need to continue to have dialysis and will need to stay in hospital for longer. It is estimated that around 50% of patients receiving this type of transplant will develop DGF.

Immediately after a kidney transplant operation, the body produces a substance called hepatocyte growth factor (HGF) which helps to repair the damage to tissue and blood vessels. However, HGF does not stay in the body for very long, and so its ability to help the body heal is limited.

Refanalin is being developed for kidney transplant patients at high risk of DGF. It acts in the same way as HGF, helping the body to repair tissue and get rid of products that can build up when the body is damaged. HGF also helps the kidneys to start producing urine. The drug is administered in an intravenous infusion within 24 hours from transplant and for the following three days. Reduced risks of developing DGF may also mean that poorer-quality donor kidneys could be used in transplant operations.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Delayed graft function following kidney transplant of a suboptimal kidney from a deceased donor

TECHNOLOGY

DESCRIPTION

Refanalin (BB-3) is a small molecule which mimics the activity of hepatocyte growth factor (HGF). The receptor for HGF is called c-Met. The HGF/c-Met pathway participates in the regulation of blood vessel formation, tissue repair and regeneration, and reducing deposition of extracellular matrix, a material produced in excess by injured tissues that causes organ dysfunction and fibrosis.[1] HGF is secreted from mesenchymal cells into the circulation and is rapidly upregulated in multiple organs after acute kidney injury (such as occurs in a transplant operation), suggesting that the HGF/c-Met signalling system targets its action to injured tissue by site-specific upregulation of its receptor. However, HGF upregulation is transient and HGF is rapidly cleared by the liver, thus having a very short systemic half-life (<4min). Supplementing HGF in the form of exogenously administered protein or gene therapy protects renal epithelial cells from both apoptotic and necrotic death and preserves the structural and functional integrity of renal tubules.[2]

Early studies with refanalin have demonstrated that it improves survival, mitigates tubular injury and death and augments renal output. Refanalin emulates the tissue-protective activity of HGF. The product also has renoprotective effects, augmenting urine output, reducing serum creatinine and blood urea nitrogen, attenuating tubular injury and tubular cell death, and promoting tubular regeneration.[2]

The intended use of refanalin is for renal transplant patients at high risk for delayed graft function (DGF) after receiving a suboptimal kidney from a deceased donor. In the phase III trial (GIFT; NCT02474667), the product is administered by intravenous (IV) infusion for 30 minutes within 24 hours after transplantation and around 24 hours after previous dosing for 3 days in a row.[3]

Refanalin does not currently have Marketing Authorisation in the EU for any indication.

Refanalin is also in clinical trials for the treatment of acute kidney injury in patients who undergo open heart surgery that uses cardiopulmonary bypass (heart-lung machine).[1]

INNOVATION and/or ADVANTAGES

If licensed, refanalin will offer a treatment option for kidney transplant patients with delayed graft function (DGF), who currently have no effective therapies available.

Refanalin also has the potential to increase the use of marginal organs and lead to shortened waiting times for transplant operations.[4]

DEVELOPER

Angion Biomedica Corp.

REGULATORY INFORMATION/ MARKETING PLANS

Refanalin was designated an orphan drug in the USA to improve renal function and prevent delayed graft function following renal transplantation in May 2010.[5]

Refanalin was awarded Fast Track designation to improve renal function and prevent delayed graft function following renal transplantation by FDA in July 2010.

PATIENT GROUP

BACKGROUND

Delayed graft function (DGF) is a common early complication following kidney transplantation from a deceased donor. It is primarily a consequence of ischaemia and reperfusion (IR) injury resulting in post-ischaemic acute tubular necrosis. The degree of IR injury is dependent on a complex interplay of pre-transplant injury and on subsequent innate and adaptive immune responses after reperfusion.[6]

There are many definitions of DGF due to the complexity of its pathophysiology. The most frequent definition is based on post-transplant dialysis requirements (at least one dialysis session during the first 7 days after transplantation). Other definitions rely on urine output, creatinine reduction, analysis of urine biomarkers or renal blood flow.[6]

The main donor factors increasing the risk of DGF are increasing donor age, donor type and quality of pre-kidney procurement care. Recipient factors influencing the risk of DGF include male gender, body mass index >30, African-American ethnicity, history of diabetes, anti-human leukocyte antigen immunisation, and requirements for dialysis before transplantation.[6]

In the short term, the main reason to prevent DGF is to avoid the need for post-transplantation dialysis. Dialysis is a choice of last resort and puts the graft at risk because of potential hypotension, risk of thrombosis, increase in hospitalisation, and worse clinical outcome.[7]

There is also a long-term detrimental association between DGF and important graft outcomes like graft survival, acute rejections and renal function.[7] Meta-analysis of 34 studies from 1988 to 2007 found that patients with DGF had a 49% pooled incidence of acute rejection compared to 35% incidence in non-DGF patients.[8]

CLINICAL NEED and BURDEN OF DISEASE

As many as 50% of cases of kidney transplant can be complicated by DGF.[6] In 2016/17 a total of 3,042 adult kidney transplants were performed in the UK, of which 2,105 (69%) were deceased donor kidney transplants.[9] A 50% DGF complication rate would therefore equate to around 1,053 cases a year.

The severe shortage of deceased donor organs available for transplantation has led to increased use of kidneys from suboptimal donors with potentially less good transplant outcome. In 2016/17, 39% of all transplants were performed using kidneys from donors categorised as high risk (compared to 29% in 2007/08).[9]

At 31st March 2017 there were 7,956 adult patients on the kidney transplant list in the UK.[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Renal replacement therapy services for adults (QS72). Updated January 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Adults Kidney Transplant Service specification. 16079/S. April 2017.
- NHS England. 2013/14 NHS Standard Contract for Adult Kidney Transplant Service. A07/S/a.
- The National Service Framework for Renal Service. Part One: Dialysis and Transplantation. January 2004.

OTHER GUIDANCE

- The Renal Association. Clinical Practice Guideline: Post-Operative Care in the Kidney Transplant Recipient. February 2017.[10]
- Kidney Disease: Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the care of Kidney Transplant Recipients: a summary. August 2009.[11]
- European Best Practice Guidelines for Renal Transplantation (Part 1). December 2000.[12]

CURRENT TREATMENT OPTIONS

The Renal Association clinical practice guidelines for post-operative care do not make any recommendations for the treatment of DGF.[10] Similarly, the KDIGO clinical practice guidelines do not have specific recommendations for DGF.[11] These guidelines recommend a biopsy is performed in a stable graft in the setting of persisting delayed graft function, and give recommendations that would be followed if a diagnosis of acute rejection is made.

European best practice guidelines for renal transplantation (2000) state that no specific treatment is necessary for post-transplant acute tubular necrosis (other than continued administration of immune-

suppressive medication, dialysis, optimal hydration and curtailed use of nephrotoxins) as long as the kidney remains viable and shows no signs of rejection. However, kidneys with DGF or acute tubular necrosis are more likely to develop acute rejection, and these patients therefore required very careful follow-up. Research has also shown that DGF on the basis of acute tubular necrosis is an independent risk factor for acute rejection and suboptimal graft function at one year.[12]

In the absence of acute rejection, specific supportive parameters remain largely unknown as to their influence on reducing the duration of DGF. Post-transplant dialysis should be offered when clinically indicated. Use of anti-lymphocyte therapy after DGF is established may not treat the DGF, but use of anti-lymphocyte therapy will reduce the rejection rate and minimise the impact of acute rejection in association with DGF.[8]

EFFICACY and SAFETY

Trial	GIFT, NCT02474667; refanalin vs placebo; phase III
Sponsor	Angion Biomedica Corp.
Status	Ongoing
Source of Information	Trial registry[3]
Location	USA
Design	Randomised, placebo-controlled
Participants	N=152 (planned); aged 18 years and older; recipient of a first kidney transplant from a deceased donor, patient has poor renal function in the first 24 hours post-transplantation
Schedule	Randomised to refanalin IV for 30 min within 24 hrs after transplantation and around 24 hrs after previous dosing 3 days in a row; or placebo IV for 30 min within 24 hrs after transplantation and around 24 hrs after previous dosing 3 days in a row.
Follow-up	Active treatment for 4 days, follow-up 1 yr.
Primary Outcomes	Severity of delayed graft function (DGF) [Time Frame: from the first day of study drug dosing (Day 1) until the last dialysis session or until Day 30, whichever comes first]
Secondary Outcomes	• Severity of DGF assessed as the duration of dialysis [Time Frame: during Days 5-30, Days 8-30, Days 15-30 and Days 22-30] • Severity of DGF assessed as the number of dialysis sessions [Time Frame: during Days 5-30, Days 8-30, Days 15-30 and Days 22-30] • Serum creatinine [Time Frame: at Day 7, Day 14, Day 30, Day 60, Day 90, Day 180 and Day 360] • Estimated creatinine clearance [Time Frame: at Day 7, Day 14, Day 30, Day 60, Day 90 and Day 180] • Estimated glomerular filtration [Time Frame: at Day 7, Day 14, Day 30, Day 60, Day 90 and Day 180] • Incidence of dialysis [Time Frame: within the first 7 days post-transplant]

	• The proportion of patients with a SCr >3mg/dL but who have not required dialysis [Time Frame: within the first 5 days post-transplant] • The proportion of patients with primary non-function (PNF), defined as a continuous requirement for dialysis for at least 60 days post-treatment [Time Frame: 60 days] • Length of hospitalization following transplant [Time Frame: 60 days] • Exploratory endpoints - serum biomarkers [Time Frame: at screening, Day 1, Day 3, Day 7, Day 14, Day 30] • Exploratory endpoints - urine biomarkers [Time Frame: at screening, Day 1, Day 3, Day 7, Day 14, Day 30]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as July 2018. Study completion date reported as July 2019.

ESTIMATED COST and IMPACT

COST

The cost of refanalin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services: possible increase in transplant operations if more suboptimal donor organs are deemed suitable due to reduced risk of DGF

☐ Decreased use of existing services: reduced length of stay in hospital and reduced need for dialysis post-transplant

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: lower cost immediately post-transplant if lower length of stay and reduced need for dialysis. Wider reduction in costs from reduced need for dialysis if more transplant operations are carried out.

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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