INTERLEUKIN 17- RECEPTOR A (IL-17RA) ON LEUKOCYTES AND TISSUE CELLS MEDIATES INFLAMMATION IN A MURINE MODEL OF CRESCENTIC GLOMERULONEPHRITIS

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**Aim:** To explore the role of IL-17RA in experimental crescentic glomerulonephritis (GN).

**Background:** Interleukin (IL)-17A and IL-17F are inflammatory cytokines which signal through IL-17 receptor A (IL-17RA), expressed on many cell types, including renal tissue cells.

**Methods:** Necrotising, crescentic GN was induced by intravenous administration of sheep anti-mouse glomerular basement membrane globulin, thereby initiating a renal injury. Mice were culled at day 21. Wild type C57BL/6 (WT), IL-17RA-/- and bone marrow chimeric mice were used.

**Results:** IL-17RA-/- mice had reduced crescent formation (WT 17 ± 3 vs IL-17RA-/-: 9 ± 3 P < 0.05), with fewer glomerular neutrophils (1.2 ± 0.1 vs 0.76 ± 0.04 cells/glomerular cross section [c/gcs]; P < 0.05), macrophages (2.0 ± 0.02 vs 1.1 ± 0.25; P < 0.05) and a trend towards fewer T cells (0.25 ± 0.1 vs 0.15 ± 0.1; P = NS). IL-17RA-/- mice had lower circulating anti-SO antibodies than WT mice (OD550 1.100; 0.3 ± 0.1 vs 0.2 ± 0.0; P < 0.05).

**Conclusion:** IL-17A/FR signalling promotes glomerular injury. Leukocyte-derived IL-17RA promotes immunity and injury, while IL-17RA on radio-resistant cells (0.25 vs 1.10; P = 0.05) may contribute to injury.

SHORT AND LONG TERM BIOLOGICAL VARIATION OF HIGH SENSITIVITY TROPONIN T (HS-TnT) AND N-TERMINAL B-TYPE NATRIURETIC PEPTIDE (NT-PROBNP) IN THE STABLE DIALYSIS POPULATION

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**Aims:** To determine the within-person/biological variation of hs-TnT and NT-proBNP in stable dialysis patients, and derive the difference between serial measurements needed to detect a clinically significant change with 90% certainty (CV%).

**Background:** hs-TnT is frequently measured in the dialysis population for the diagnosis of acute cardiac events, and NT-proBNP is an emerging biomarker of long-term cardiac risk, but their underlying biological variation in this setting is unknown, leading to misinterpretation of serial measurements.

**Methods:** Multicentre, prospective cohort study. 53 prevalent HD and PD patients (N = 111) were assessed 10-times: weekly for 5-weeks then monthly for 4-months. Assessments were conducted at the same dialysis-cycle time point and entailed clinical review, bioimpedance spectroscopy, ECG, hs-TnT and NT-proBNP testing. Batched samples underwent duplicate analysis in a single-run. Patients were excluded if they underwent a change in cardiac medication, dialysis prescription, ischaemic symptomatology, extracellular volume >1L, new arrhythmia or hospitalisation between visits. Between-person(CV%) and within-person(CV%) coefficients of variation were estimated using nested analysis of variance.

**Results:** 136-weekly and 111-monthly intervals from 42 patients were able to be included (age 59 ± 15 yrs, coronary-artery disease = 22%, LV ejection fraction = 60 ± 7%, diastolic dysfunction = 86%). For NT-proBNP:

Median = 1974 pg/mL, CV% = 152%, CV% naïve = 27% and CV% naïve = 35%, RCV naïve = 46%–84%, RCV naïve = 54%–120%, CV% = 0.23. For hs-TnT: Median = 34 ng/L, CV% = 81%, CV% naïve = 7.9% and CV% naïve = 12.6%, RCV naïve = 17%–22%, RCV naïve = 25%–34%, CV% = 0.16. CV% was consistent across cardiac comorbidity subgroups.

**Conclusions:** Serial NT-proBNP levels need to double or halve and hs-TnT levels must increase by 20–34% or fall by 17–25% to confidently exclude change due to analytical & biological variation alone. The low CV% in both implies the best strategy for applying these biomarkers in dialysis is relative change monitoring after a baseline estimate rather than comparing results to reference intervals.
This study establishes the involvement of Syk in antibody-mediated rejection in a specific model of AMR. CC-482417 reduced serum DSA levels by 60% (P < 0.01) and ECP by 0.6% (P = 0.01) from high- to low-salt period. At 6 months, SBP/DBP reductions were maintained (increase of 1.3% (95% CI -8.7 to 3.1) mm Hg (P = 0.05) when compared with low-salt period). As was ECP (P < 0.05). Median protein/albumin excretion were reduced by 45-50% in period-1 and this was maintained at 6-months (P = 0.05).

Conclusions: Sodium restriction considerably reduced BP; ECP and proteinuria in CKD patients, and, with the assistance of ongoing dietary-counselling by an accredited dietitian, these benefits were maintained at 6-months.

Blockade of spleen tyrosine kinase (Syk) inhibits antibody-mediated rejection in rat renal allografts

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Aim: To determine whether spleen tyrosine kinase (Syk) plays a role in acute renal allograft rejection.

Methods: Kidney allografts induce strong antibody responses which contribute to graft rejection. Syk is involved in the antibody response (via B-cell receptor signalling) and antibody-dependent activation of macrophages and neutrophils (via Fcγ receptor signalling), whereas Syk is not expressed by T-cells. However, the role of Syk in these responses has not been investigated in allograft rejection.

Results: Vehicle treated recipients developed severe allograft failure (serum creatinine 304 ± 130 vs 46 ± 7 µmol/L in isograft; P < 0.001). Histologic damage included glomerular and peritubular capillaritis, tubular injury (tubulitis, necrosis, dilation) affecting 90% of tubules, and T-cell, macrophage and neutrophil infiltration. Immunostaining identified Syk activation in infiltrating leukocytes. Allografts showed IgG and IgD deposition and circulating donor-specific antibodies (DSA) were identified by flow cytometry. CC-482417 improved allograft function (serum creatinine 149 ± 18 µmol/L; P = 0.05 vs vehicle), with reduced tubular damage (47 ± 19% P = 0.001) and a reduction in capillaritis. CC-482417 did not affect T-cell infiltration or activation (IL-2, granzyme B, IL-2Ralpha). Interestingly, CC-482417 reduced serum DSA levels by 60% (P < 0.01). Conclusion: This study establishes the involvement of Syk in antibody-mediated, but not T-cell mediated, acute renal allograft rejection. Further studies should examine Syk inhibition in a specific model of AMR.

Calciprotein-associated fetuin-A concentration is associated with all-cause mortality in patients with pre-dialysis CKD

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Aim: To assess the effects of Dendritic Cell (DC)-targeted CXCR1 vaccination in the prevention of macrophage infiltration and attenuation of atherosclerosis in apo-E/- mice.

Background: Monocytes/macrophages are involved in the pathogenesis of atherosclerosis. CXCR1 chemokine ligand 1 (CX3CL1/Fractalkine) and its receptor CX3CR1 have been identified to have an important role in the migration and recruitment of monocytes during the pathogenesis of atherosclerosis.

Methods: DC-targeted and control vectors with CX3CR1 (DEC-CX3CR1/con-CX3CR1) were generated. Apo-E-/- mice were vaccinated weekly (3x). Anti-CXCR1 antibody was determined by ELISA. Whole aortas were dissected at 34 weeks of age. Severity of atherosclerosis, macrophage infiltration and lipid deposition were examined histologically.

Results: DEC-CX3CR1 vaccinated mice had high levels of anti-CXCR1 antibodies (Abs 1.1), Con-CXCR1 vaccinated mice also had increased antibodies (Abs 0.85), compared to controls (Abs 0.13) (p < 0.001). DEC-CX3CR1 and Con-CXCR1 vaccinated mice demonstrated a decreased plaque size (39% vs 46% of luminal area) as compared to the control (58%) in brachiocephalic artery (p<0.01, p<0.05). In the aortic arch, DEC-CX3CR1 vaccinated mice showed a significantly decreased plaque size (7.5%) compared to Con-CX3CR1 vaccinated mice (16%) and control (18%), (p<0.05, p<0.01 respectively). Both DEC-CX3CR1 and Con-CXCR1 vaccinated mice had a significantly decreased infiltration of macrophages (19% vs 21% of plaque area) into the atherosclerotic plaques in comparison to controls (40%, p<0.05, p<0.001 respectively). DEC-CX3CR1 vaccinated mice revealed a significantly lower lipid deposition level (9% of plaque area) within the atherosclerotic plaques compared to Con-CXCR1 mice (14%, p<0.05) and controls (16%, p<0.001).

Conclusions: DC-targeted CXCR1 vaccination induced specific antibodies that limit macrophage infiltration into atherosclerotic plaques suggesting a potential therapeutic role in atherosclerosis.
BENEFITS AND COSTS OF AN ACCEPTABLE HUMAN LEUKOCYTE ANTIGEN MISMATCH PROGRAM IN AUSTRALIA

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Aims: To determine the benefits and costs of implementing an acceptable mismatch program in Australia.

Background: Implementation of an acceptable mismatch program in Europe has improved access to transplantation for highly-sensitised patients on the deceased-donor waiting list, but the benefits and costs of a similar program in Australia is unclear.

Methods: Using a third party perspective, two probabilistic decision analytical models were developed to compare 1) an eplet-defined acceptable mismatch and 2) and eplet/LumineX-defined acceptable mismatch program with the current deceased-donor allocation model in Australia (n = 10,000, age 18+). The model terminated when all transplant recipients were deceased.

Results: Compared with current allocation, an eplet-defined acceptable mismatch model reduces average waiting time for 4 of 28 (14%) highly-sensitised recipients by 34 ± 22 months (p = 0.056), with an average gain of 1.12 life-days and $62.2 savings per patient; whereas an eplet/LumineX-defined acceptable mismatch model reduces the average waiting time for 12 of 23 (52%) highly-sensitised recipients by 37 ± 33 months (p = 0.033), with an average 6.06 life-days gained and $2,805 savings per patient. Average increase in waiting time for reallocated recipients in the eplet and eplet/LumineX models were 12 ± 9 and 15 ± 18 months respectively. Among non-highly-sensitised patients on the waitlist, there was a reduction of 0.09 life-days and $59 excess cost in the eplet-defined acceptable mismatch model and a reduction of 0.60 life-days and $374 excess cost in eplet/LumineX-defined acceptable mismatch model.

Conclusions: The integration of an acceptable mismatch program into the deceased-donor kidney allocation reduces waiting-time and provides modest health benefits and cost savings for highly-sensitised patients without incurring significant reduction in overall health benefits and extra costs for non-highly-sensitised candidates on the waitlist.

THE ASSOCIATION BETWEEN GLOMERULAR FILTRATION RATE ESTIMATED BY MULTIPLE METHODS AT DIALYSIS COMMENCEMENT AND PATIENT SURVIVAL IN THE IDEAL TRIAL

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Background and Aims: The Initiating Dialysis Early and Late (IDEAL) study demonstrated that planned early or late initiation of dialysis, based on the Cockcroft and Gault (CG) estimation of glomerular filtration rate (eGFR), was associated with identical clinical outcomes. This study was a pre-specified analysis examining the association of all-cause mortality with eGFR, measured by the CG, Modification of Diet in Renal Disease (MDRD) or the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formulae at dialysis commencement.

Methods: IDEAL trial participants were allocated into tertiles according to the CG, MDRD and CKD-EPI formulae at dialysis commencement. The patient survival was assessed using the Kaplan-Meier method.

Results: There was no difference in survival among patients when stratified into tertiles of GFR according to the CG formula. However, there was a significant survival benefit in the tertile of patients starting dialysis with the lowest eGFR when the MDRD or CKD-EPI formulae was applied (p < 0.01), independent of correction for body surface area. An increased hazard ratio for death was observed in older females and patients with diabetes and cardiovascular disease independent of the formula used.

Conclusion: Discrepancies exist in the relationship between eGFR at dialysis commencement and mortality in patients with stage 5 CKD depending on the formula used. Patients commencing dialysis with a higher eGFR were more likely to be older, Caucasian and have a history of ischemic heart disease, suggesting that observational studies demonstrating a survival benefit in patients who start dialysis ‘late’ is due to reduced comorbidity.

SLOW-MELT NACIN WITH ADJUVANT PHOSPHATE BINDERS IN DIALYSIS PATIENTS

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Aims: To summarise the current evidence on the impact of buttonhole cannulation on infection rates.

Background: Publications in the last decade have reported the utilization of buttonhole cannulation (BH) method for vascular access, especially in the home haemodialysis population. Some have reported an association with increased infections in comparison to ropeladder (RL) cannulation, although definitive evidence is lacking.

Methods: We searched Medline, EMBASE, the clinical trials registry (www.clinicaltrials.gov) and reference lists of review articles and trials for cannulation studies in maintenance haemodialysis patients comparing BH with alternative cannulation methods without language restriction. “Renal dialysis” and “catheterization” were used as MedSH terms while “buttonhole cannulation” as a text term. Randomised clinical trials (RCT’s) and observational studies between 1950 and 17 May 2013 were included. The primary outcome was access-related infection. Relative risk (RR) or incidence rate ratios (IRRs) with associated 95% confidence intervals (CI) were calculated or reported IRR used. Random effects models were used to calculate overall effect estimate and 95% CIs.
Utility of "back up" arterio-venous fistulas in patients on peritoneal dialysis and use of central lines: A comparison between two Australian centres

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Aim: To study utility of back-up arterio-venous fistulae (AVF) in patients initiated on peritoneal dialysis (PD) to determine the rates of central venous catheter (CVC) use in patients requiring conversion to haemodialysis (HD).

Background: There is limited data on benefit of back-up AVF in patients treated with PD and it has been argued that these may not be usable at the time of HD transfer. There is therefore a high rate of CVC use in this population when they require transfer to HD.

Methods: We retrospectively analysed data on patients transferred to HD from PD, between January 2008 and December 2012 at both Royal Adelaide Hospital (RAH), where a policy of AVF in most PD patients is followed, and Princess Alexander Hospital (PAH), where only patients at risk have back-up AVF created.

Results: Of the 142 patients at RAH, 33 (23%) patients required transfer to HD. 25 patients had back-up AVF, which was successfully used in 22 patients (88%). CVC had to be used in 3 patients (12%) at the fistula was dysfunctional. The CVCs used during transfer at RAH were 11 (33%) of the 232 patients at PAH. 70 (30%) required transfer. AVF was utilised in 26 (37%) patients, whereas a CVC had to be used in 44 (61%) patients. Routine creation of AVF in PD patients was associated with a catheter usage rate of 24% (RAH) as compared to a rate of 61% (PAH) in a centre where this is not done (P = 0.0006, Fisher’s exact test).

Conclusion: Routine creation of a back-up AVF in all PD patients is sustainable and results in a much lower rate of CVC use on HD transfer.

Fetuin-containing calciprotein particle levels can be reduced by dialysis, sodium thiosulphate and plasma exchange: potential therapeutic implications

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Aim: To determine whether, if any, clinical treatment strategies cause a reduction in Fetuin-A (Fet-A) calciprotein particles (CPP) in dialysis patients.

Background: Fetuin-A is an important regulator of physiological and pathological mineralisation. Fetuin-A (Fet-A) has been shown to protect from ectopic mineralisation. In patients with chronic inflammation and with chronic renal impairment, Fet-A is detectable within large macrovascular complexes called calciprotein particles (CPP). These are composed of nanocrystals of calcium phosphate surrounded by a predominantly Fet-A protein ‘shell’. CPP formation may protect cells against the pro-inflammatory and pro-apoptotic effects of naked crystalline calcium phosphate, but may themselves be proinflammatory. We have previously demonstrated that in calciphylaxis, a condition associated with severe vascular calcification and a very poor prognosis, a very high proportion of serum fetuin-A circulates as CPP (CPP%). Treatment of the condition is hindered by the lack of a reliable target to monitor and we wonder if serum CPP% might be a useful biomarker.

Methods: We determined whether include increased duration/frequency of haemodialysis (HDx), sodium thiosulphate (STS) infusion, plasma exchange (PEx) or transplantation were associated with a sustained reduction in CPP%.

Results: HDx reduces serum CPP% but not sustainably so. The addition of STS infusion during HDx further reduced CPP%, but infusion between HDx sessions had no significant sustained reduction. PEx provided additional benefit, reducing CPP% between HDx sessions. Transplantation resulted in sustained lower levels of CPP%.

Conclusion: CPP% may be a modifiable marker of mineral stress. Experiments are being conducted to determine whether CPP are directly involved in the pathology of vascular calcification.

Use of stents in haemodialysis fistulae: success and long term follow-up

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Aim: Endovascular stent deployment is used to treat dysfunctional haemodialysis fistulae characterized by resistant or recurrent stenosis and pseudoneuromas. This study aims to report the procedural success, complication rate and long-term patency of stents in haemodialysis fistulae at a single centre.

Background: The use of self-expandable bare metal and covered stents has been described in the literature with varying degrees of success.

Methods: Between 2008 and 2012, 50 procedures (9 for pseudoneuromas, 41 for resistant or recurrent stenoses) were performed in 42 patients at a single centre. Clinical and radiological information collected during this period was reviewed retrospectively. Post-intervention primary and secondary (cumulative functional) patency rates were determined using Kaplan-Meier analysis. Patients were censored for death, loss to follow-up and transplantation.

Results: The clinical and anatomical success rate was 98% (49/50). Minor complications that did not affect procedural success occurred in 3 instances. A major complication leading to access loss occurred in one procedure. Post-intervention primary patency rates at 6, 12 and 18 months were 52%, 24% and 10% respectively. Post-intervention secondary patency rates at 6, 12 and 18 months were 98%, 92% and 92% respectively, with an additional 1.7 procedures per patient.

Conclusion: The use of stents in haemodialysis fistulae provides excellent functional patency of the dialysis fistulae but repeated procedures are required to maintain secondary patency.

Upper arm fistulae and multiple stenoses influence haemodialysis arteriovenous fistulae patency after balloon angioplasty

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Aim: Patenty after percutaneous balloon angioplasty (PTA) for haemodialysis fistula stenosis is highly variable. This study aimed to assess factors associated with patenty following first episode of treatment with PTA.

Background: Restenosis recurs commonly after PTA. Previous studies have shown that some intrinsic fistula and biochemical factors may influence patency after PTA.

Methods: We retrospectively reviewed all endovascular procedures performed by nephrologists between 2007 and 2012 at a single centre. Anatomical, clinical, biochemical and medication information was subjected to cox regression analysis to identify factors influencing post-intervention patency.

Results: 120 patients were identified as having first episode treatment with PTA. During a median follow-up period of 22.66 months (5.24–53 months), 171 follow-up procedures were performed. Post-intervention primary patency rates at 6, 12 and 18 months were 46%, 25% and 15% respectively. Cumulative (functional) patency rates at 6, 12 and 18 months were 97%, 94% and 92% respectively with 1.4 additional procedures per patient. In univariate cox regression analysis, the presence of multiple lesions (p = 0.037) was associated with early restenosis at 6 months, while upper arm fistulae were associated with early restenosis (p = 0.004) and shorter primary patency (p = 0.001). Other anatomical characteristics (fistula age, lesion length, pre-procedure stenosis), clinical history
At first dialysis Western Sydney: early referral is chronic kidney disease clinical outcomes after arteriovenous eGFR before becoming established on HD. While early AVF creation is an important goal, we demonstrate at 3, 6 and 12 months respectively, 20%, 44% and 56% of patients with was 12.5 mL/min/1.73 m², 74% were referred with a GFR of 15 mL/min/1.73 m² and 92% with a GFR of 20 mL/min/1.73 m² or less. To review characteristics and outcomes for patients referred to a comprehensive predialysis programme in Western Sydney. This study aims to determine outcomes and optimal timing for AVF creation in CKD patients. The proportion of patients commencing dialysis with permanent access. Earlier referral is associated with a higher chance of commencing dialysis with permanent access. A mature arteriovenous fistula (AVF) at the start of dialysis reduces morbidity, mortality and costs compared to a central venous catheter (CVC). In 2005, less than 38% of our patients commenced haemodialysis with an AVF and Central Line Associated Blood Stream Infection (CLABSI) rate associated with our haemodialysis CVCs was 3.5/1000 catheter days. A multi-pronged intervention was developed with focus on a renal access co-ordinator to expedite a “fistula first” approach and reduce complications associated with our haemodialysis CVC use by targeting incident (first dialysis) catheter rates and CLABSI rates. Outcome was assessed by 1. Proportion of patients starting dialysis with a CVC. 2. Tunnelled Haemodialysis associated CLABSI rates per 1000 catheter days. 3. Proportion of patients on maintenance dialysis with a CVC. 4. Non-tunnelled haemodialysis catheter total yearly dwell days. 5. Proportion of prevalent patients and incident patients with AVF. The proportion of patients commencing haemodialysis via a CVC dropped from 62% in 2005 to 34% in 2012. The CLABSI Rate associated with tunneled Haemodialysis catheter use dropped from 3.5/1000 days in 2005 to 0/35/1000 days in 2012. The percentage of patients on maintenance haemodialysis via a CVC dropped from 13% in 2005 to 9% in 2012. The non-tunnelled CVC line days per year dropped from 1330 line days/yr in 2006 to 220 line days/yr in 2012. The percentage of incident patients with AVF improved from 15% in 2007 to 35.7% in 2012, and prevalence rate from 76% to 88%.

Factors influencing haemodialysis arteriovenous fistula patency after balloon angioplasty: a systematic review

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Aim: Percutaneous transluminal angioplasty (PTA) is an established treatment for haemodialysis fistula stenosis. This study aimed to systematically review evidence for factors associated with patency after percutaneous transluminal angioplasty (PTA).

Background: The effects of patient comorbidity, demographic, biochemical and anatomical characteristics, with initial PTA success and post-intervention patency have not previously been summarised.

Methods: We searched databases to identify studies assessing patency after PTA in haemodialysis fistulae. Studies of immature or thrombosed fistulae or other dialysis access were excluded. Quality of studies was assessed using a modified validated checklist. Outcomes assessed were post-intervention primary and secondary patency, restenosis at 6 months, technical and clinical success, assisted primary patency and mean interval or frequency of endovascular interventions during follow up. Findings were summarized descriptively.

Results: We included 12 single-centre studies of 1,120 participants with 1,281 fistulae. Follow-up ranged from 3 days-10years. Shorter primary patency was seen with more recent fistulae (4 studies), longer stenosis length, upper arm fistulae (2 studies), small inflow artery diameter, arteriovenous anatomic site and history of previous endovascular interventions (1 study each). Shorter secondary patency was seen with increased patient age (2 studies), and more recent fistulae (1 study). Early restenosis was associated with diabetes (3 studies), HbA1c, low-density lipoprotein, and asymmetric dimethylarginine (1 study each). Technical success was reduced for upper arm fistulae and high-grade stenoses (1 study), while clinical success of PTA was more likely in stenotic compared to thrombosed fistulae (1 study).

Conclusion: Fistula characteristics and diabetes may be associated with poor PTA outcomes, however evidence is inconclusive, and the role of metabolic and inflammatory markers is unclear.