LATE BREAKING ORAL

LBA01 - ORAL LATE BREAKING

LBA001 IN SITU SKIN REGENERATION THROUGH INDUCTION OF SKIN ALLOGRAFT CHIMERISM BY MOBILIZING HOST ENDOGENOUS STEM CELLS

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Introduction: Treatment of large full-thickness burns is a major military and civilian challenge due to limitations of autogenous skin, wound infection and severe metabolic stress. While modern treatment provides survival from severe burns, the healing leaves an imperfect result with scarring, disfiguration and loss of critical skin functions. In response to these challenges, we proposed to induce in situ skin regeneration through repopulation of skin allografts using our novel stem cell mobilizing therapy that enabled long-term liver and kidney allograft survival with short-term treatment and freedom from immunosuppression.
Methods: GFP+ transgenic Lewis rat recipients received 3 × 3.5 cm fully MHC-mismatched Dark Agouti full-thickness skin allografts. Transplanted animals were treated with a combination of AMD3100 (1 mg/kg) and low-dose FK506 (0.1 mg/kg) (AF) subcutaneously every other day ($n = 8$) or the same amount of saline ($n = 10$) for 8 weeks. Skin biopsies obtained at different time points were stained for stem cell (CD133, CD34), host (GFP+) and regulatory T cell markers.
Results: In the control group, skin allografts were rejected within 14 days after transplantation. Strikingly, the AF combination treatment prolonged skin allograft survival and skin allografts maintained for over 2 months. At three weeks, host-derived CD133 stem cells and $FOXP3^+$ cells were dramatically increased in skin allografts and some of donor epithelial tissues were repopulated by host-derived cells (GFP+). At 6 weeks, host-derived *de-novo* white hair follicle regeneration was visible, as was donor-derived black hairs confirming skin allograft chimerism.
Conclusion: In situ skin regeneration can be realized by host repopulation of skin allografts through pharmacological mobilization of endogenous bone marrow stem cells with a mechanism similar to host repopulation of liver and kidney allografts.

LBA002 LIVER PRE-ISCHEMIC HOPE PRE-CONDITIONING: NEW CONCEPT TO IMPROVE GRAFT PRESERVATION

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Background: Optimizing liver grafts preservation is a very important challenge to improve their quality. End-ischemic hypothermic oxygenated perfusion (HOPE), a promising machine perfusion protocol, seems to decrease cold ischemia related liver injury. However, the potential benefits of the pre-ischemic HOPE have not been investigated yet. We compared the ischemia-reperfusion injury (IRI) after end-ischemic or pre-ischemic HOPE treatments.
Methods: Rat livers were either preserved 10 h in static cold storage (SCS) (Control) or perfused 2 hours with HOPE protocol prior to (HOPE-PRE) or after (HOPE-END) 8 h of SCS. At the end of the SCS, all livers were re-perfused 2 h in a normothermic *ex vivo* perfusion system (37°C). Hepatic injury was evaluated during reperfusion (transaminases and lactates). Ischemia-reperfusion injury markers expression (Casp-3, apoptosis inducible factor (AIF), Beclin-1, Bcl2, high mobility group box 1 (HMGB1), syndecan-1, heparan sulfate, GSH/GSSG) were determined in tissue homogenates at the end of the reperfusion. Mitochondrial injury marker flavin adenine dinucleotide (FAD) was assessed
Results: HOPE-PRE significantly decreased the liver injury compared to HOPE-END as demonstrated with a lower transaminases release. Better liver functionality in HOPE-PRE group was consistent with a decreased of nuclear injury (HMGB1) and apoptosis (Casp-3 and AIF) associated with a higher autophagy proteins expression (Beclin-1 and Bcl-2). After 1 h of HOPE-PRE treatment, mitochondrial function (FAD) was significantly improved as compared to HOPE-END, which was correlated with an increase in antioxidant Glutathione reduced form (GSH) over its oxidized form (GSSG). HOPE-PRE also improved the protection of the liver endothelial glycocalyx components (syndecan-1 and heparan sulfate) leading to higher production of nitric oxide compare to HOPE-END
Conclusions: Both HOPE protocols decrease IRI at reperfusion. However, doing HOPE-PRE, provides better hepatic protection by improving mitochondrial functionality and glycocalyx integrity.

LBA003 EVALUATION OF CLAZAKIZUMAB (ANTI-IL-6) FOR TREATMENT OF KIDNEY TRANSPLANT RECIPIENTS WITH CHRONIC & ACTIVE ANTIBODY MEDIATED REJECTION

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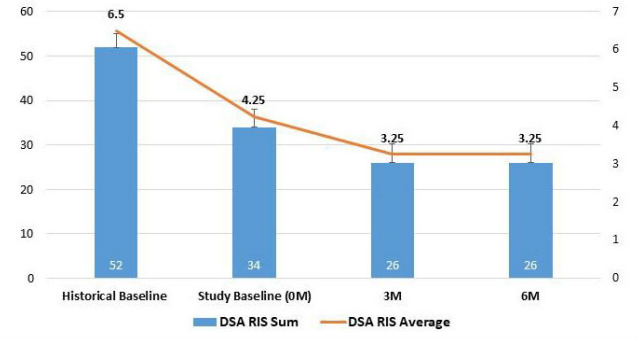
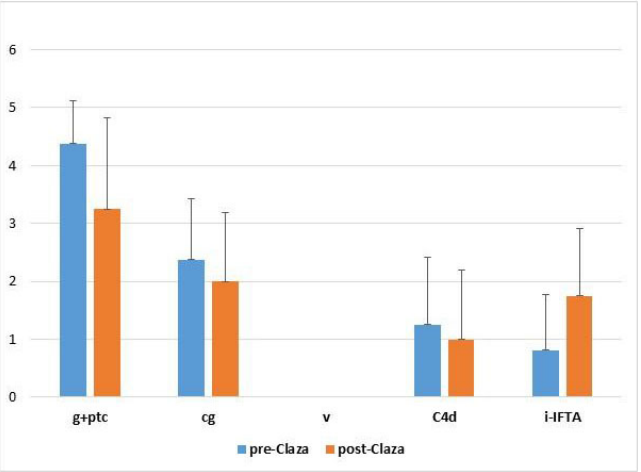
Introduction: Highly sensitized (HS) patients are at an increased risk for chronic antibody mediated rejection (cABMR) and graft loss. Therapeutic options to prevent and treat cABMR are limited. Here, we report our preliminary experience using clazakizumab, a novel IL-6 inhibitor, in HS patients with cABMR + transplant glomerulopathy (TG).
Methods & Materials: Since February 2018, 10 adult patients with biopsy proven cABMR+TG and DSA+ were enrolled in a phase I/II, single-center, open-label exploratory study. All patients received clazakizumab 25 mg subcutaneous injections monthly for 6 doses followed by a 6 month protocol biopsy. Patients were monitored for DSA relative intensity scores [(RIS); 0 = No DSA; 2 = <5000 MFI (weak); 5 = 5000-104 MFI (moderate);10 = >104 MFI (strong)], eGFR, CRP levels, cytokine levels and IgG.
Results: All patients showed marked reductions in CRP levels post-clazakizumab (1.21 ± 1.30 at 0 M v 0.3 ± 0.12 at 6 M, p = 0.07). 100% of patients' DSAs were class II (DQ, 75%). After 6 months, reductions in mean DSA-RIS were observed (6.50 ± 3.07 historical vs 3.25 ± 4.27 at 6 M, p = 0.637) (Figure 1) while mean GFRs remained stable (41.35 ± 8.54 ml/min at 0 M vs. 43.75 ± 9.63 ml/min at 12 M, p = 0.6). Six month biopsies exhibited the following changes in Banff scoring: g+ptc 4.38 0 M to 3.25 at 6 M (p = 0.090), cg 2.38 0 M to 2.00 at 6 M (p = 0.518), v 0 to 0 at M0 and 6 M, C4d 1.26 0 M to 1.00 at 6 M (p = 0.678), i-IFTA 0.813 0 M to 1.75 at 6 M (p = 0.101) (Figure 2). Treg cells tended to increase at 3 M. No serious adverse events have occurred to date. Molecular microscope analysis of pre- &





post-anti-IL 6 biopsies showed improvement or stabilization of gene scores in most patients.
Conclusions: cABMR+TG patients treated with clazakizumab showed stabilization of renal function and improvements in DSA score. Although not significant and a small sample size, biopsy findings showed trends in reduced g+ptc, cg and C4d scores. Larger controlled studies will be necessary to properly evaluate the potential benefits of clazakizumab in treatment of cABMR.

LBA004 EVALUATION OF THE SAFETY AND TOLERABILITY OF CLAZAKIZUMABA ® (ANTI-IL-6 MONOCLONAL) FOR DESENSITIZATION IN HIGHLY-HLA SENSITIZED ESRD PATIENTS (NCT 03380962)

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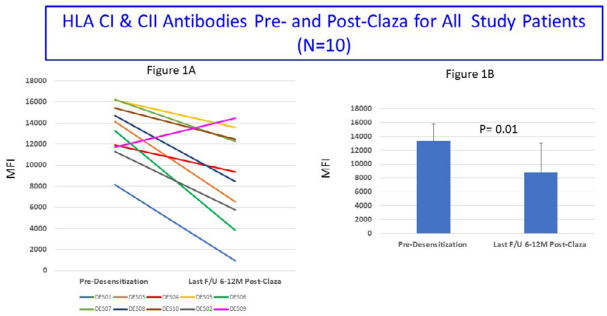
Background: Clazakizumab (Vitaeris Inc.) is a humanized monoclonal antibody aimed at the cytokine IL-6. Here we undertook a single center, Phase I/II open label pilot study, to assess safety and efficacy of anti-IL-6 as a desensitization agent in highly-HLA sensitized (HS) patients.
Methods/Materials: From March to November 2018, 10 HS patients (cPRA > 50%) received plasma exchange (PLEX) x5 sessions followed by IVIg 2 gm/kg × 1. One week post-IVIg, the patients received anti-IL-6, 25 mg SC Q4W × 6 doses w. monitoring of HLA antibody levels and other immune parameters. Study end point was transplantation by day 270 post-Rx. If transplanted, patients received 6 additional doses of anti-IL-6, with a 6-month protocol biopsy. The primary end point was reduction of HLA antibodies from baseline. All transplanted HS patients received induction with alemtuzumab and were maintained on tac/mmf/pred taper.
Results: The MFI of HLA CI & II antibodies pre- & post-claza for all study patients is shown (Figure 1A). The mean MFI pre-desensitization was 13,290 ± 2430 and post-claza was 8760 ± 4260 (Figure 1B) (p = 0.01). Previously, we noted that anti-HLA antibodies tended to rebound by ~1-3 months after PLEX/IVIg. Here, with monthly anti-IL-6, MFI values remained stable and did not rebound compared to pre-desensitization. Eight transplants (80%) were performed to date. Six of 8 patients (75%) had FCMX+ & DSA+ at transplant. One patient (12.5%) had biopsy proven chronic active ABMR @ 3 M post-transplant. SevenSAEs occurred in 5 patients, all felt unrelated to anti-IL-6. These included wound dehiscence (1), hematuria and UTI (1), thrombosis w. graft loss (1), perinephric fluid collection (2), biopsy proven chronic active ABMR (1) and bacteremia prior to 1st dose of study drug (1).
Conclusions: Anti-IL-6 appears promising as a potential desensitization agent when used with PLEX+IVIg. This treatment has a significant impact on reducing MFI levels of HLA antibodies; thereby increasing transplant rates for 8 of 10 HS patients with low risk for antibody rebound and ABMR.



LBA005 TRANSFORM STUDY (NCT01950819): APPLICATION OF THE IBOX CLINICAL TRIAL SIMULATION TOOL TO PROJECT LONG-TERM KIDNEY ALLOGRAFT OUTCOME

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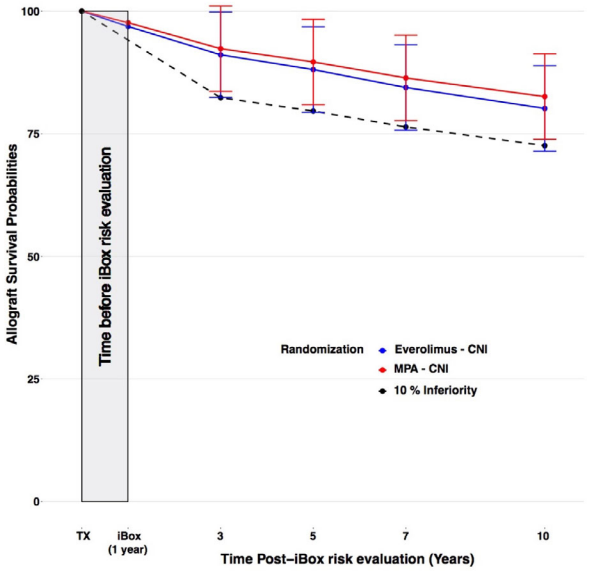
Background: The development of pharmaceutical agents in transplantation is currently limited by long waits for hard endpoints. We sought to use a risk stratification system in a large randomized control trial (RCT) and determine individual patient long-term graft survival and eGFR decline.
Methods: We used validated data from the TRANSFORM trial (NCT01950819), a RCT that compares kidney transplant recipient to receive everolimus with reduced-exposure calcineurin inhibitor (CNI) or mycophenolic acid (MPA) with standard-exposure CNI. We applied the iBox system (NCT03474003), an integrative and validated risk score which used the parameters measured at 1 year after randomization (primary end point time line) and projected patient's individual long-term allograft survival.
Results: A total of 1872 patients (940 in the everolimus arm and 932 in the MPA arm) reached the 1 year after transplant primary endpoint.

Figure 1: Projected long term allograft survival between the everolimus and MPA arms using the iBox clinical trial simulation tool



Mean projected allograft survival				
Everolimus - CNI	94.2%	91.2%	87.6%	83.3%

Mean estimated glomerular filtration rate was 55.5 ± 19.9 mL/min/1.73 m2 in the everolimus arm vs 56.1 ± 19.0 in the MPA arm. The mean protein/creatinine ratio was 0.33 ± 0.68 g/g in the everolimus arm vs 0.25 ± 0.62 in the MPA arm. The incidence of active-ABMR and acute-TCMR of 7.1% and 7.2% in the everolimus arm *vs* 6% and 7.1% in the MPA arm. The incidence of circulating anti-HLA DSA was 13.4% in the everolimus arm *vs* 14.6% in the MPA arm. These immunological, functional and histological parameters were entered into the iBox risk prediction system, which translated to an overall patient graft survival at 3, 5 and 10 years after randomization of 94.2 *vs* 94.7% %, 91.2% *vs* 92.0% and 83.3% *vs* 84.9% in the everolimus and MPA arms respectively (95% CI −3.1% to 0.2%, below the non-inferiority margin of 10%) Figure 1.

Conclusions: The iBox system confirms the non-inferiority of everolimus vs MPA 10 years after patient's randomization in the RCT. Given the unmet need for surrogate end point for clinical trials, this study shows the potential of a clinical.

LBA006 IL-10-SPECIFIC AUTOANTIBODIES PREDICT MAJOR ADVERSE CARDIOVASCULAR EVENTS IN KIDNEY TRANSPLANTED PATIENTS

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Background: End-stage renal failure is associated with persistent systemic inflammation. The aim of this study was to investigate if systemic inflammation at the time of kidney transplantation is linked to poor graft survival, major adverse cardiovascular events (MACE), and increased mortality, and if these processes are modulated by naturally occurring cytokine-specific autoantibodies (c-aAbs), which have been shown to regulate cytokine activity *in vitro*.

Materials and Methods: Serum levels of cytokines, high-sensitivity C-reactive protein (hsCRP) and c-aAbs specific for interleukin (IL)-1α, tumor necrosis factor (TNF)-α, IL-6, and IL-10 were measured at the time of transplantation in a retrospective cohort study of 619 kidney transplanted patients with a median follow-up of 4.9 years (range 1.2 to 8.2 years).

Results: Systemic inflammation was associated with all-cause mortality in simple and multiple Cox regression analyses. IL-10-specific c-aAbs were associated with MACE after transplantation, suggesting that IL-10 may be a protective factor. Similarly, patients with a history of MACE before transplantation had lower levels of TNF-α-specific c-aAbs, hence we hypothesized that TNF may be a risk factor of MACE.

Conclusion: These findings support that pro-inflammatory activity before transplantation is a pathological driver of MACE and all-cause mortality after transplantation. This information adds to pre-transplantation risk estimation in renal transplant candidates.

LBA008 INCIDENCE OF DE NOVO AND RECURRENT GLOMERULONEPHRITIS POST RENAL TRANSPLANTATION IN THE UNITED KINGDOM: USE OF TEXT MINING TO ASSESS UNSTRUCTURED DATA IN A LARGE COHORT

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Background: The National Institute for Health Research Informatics Collaborative aims to support the development of catalogued, comparable and comprehensive flows of patient data for research. The Transplantation theme has brought together four large UK renal transplant centres. The increasing use of electronic health records provides a unique opportunity to unlock the potential of large amounts of clinical data stored in these systems. Computer software such as text mining allows extraction and standardisation of large volume unstructured clinical data. To demonstrate utility, an exemplar project to assess the incidence of recurrent glomerulonephritis has been performed. While glomerulonephritidies are an important cause end stage kidney disease, the incidence of individual sub-types post transplanation is low thus requiring a large data set for study.

Methods: Patients transplanted at the centres between January 2005 and October 2016 were included. For patients who received more than one transplant during this period only the first transplant was considered. Demographic data was collected on donor and recipient. In order to establish the presence of glomerulonephritis (GN) post transplanation, histopathology reports from transplant kidney biopsies were collected. Open access text mining software (GATE) was trained to extract a positive diagnosis of four types of GN, namely IgA nephropathy, Focal and Segmental Glomerulosclerosis, Membranous and Mesangiocapillary. All positive cases were then clinically assesed to exclude false positives.

Results: Data was collected on a total of 7623 recipients. Kaplan-Meir plots of allograft survival were constructed to compare survival between the four GNs.

Conclusions: Use of computer software allows assesment of large volume unstructured clinical data, which would otherwise be impossible due to the large amount of Clinician time required to standardise it. This first study in a UK population confirms that IgA is the commonest GN post transplantation. Missing cause of ESRD prevented incidence of recurrence to be estimated.