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Chiesi

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En esta presentación puede haber mención a datos científicos que no están aprobados en el registro. Por favor, consulte la ficha técnica. Las opiniones expresadas en esta presentación corresponden únicamente a quienes las emiten y no representan necesariamente las opiniones de Chiesi España S.A.U.

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DESENSIBILIZACIÓN, INMUNOTOLERANCIA, NOVEDADES EN INMUNOSUPRESIÓN, HISTOCOMPATIBILIDAD, BIOMARCADORES, INFECCIONES, CUIDADOS PALIATIVOS

BEATRIZ RODRÍGUEZ CUBILLO, NEFROLOGÍA TRASPLANTE.

HOSPITAL CLÍNICO SAN CARLOS

DESENSIBILIZACIÓN

Kidney Immunosuppression: Desensitization

03:00pm - 04:20pm Pacific - June 4, 2023 | Room: Room 4 Upper Level (San Diego Convention Center)

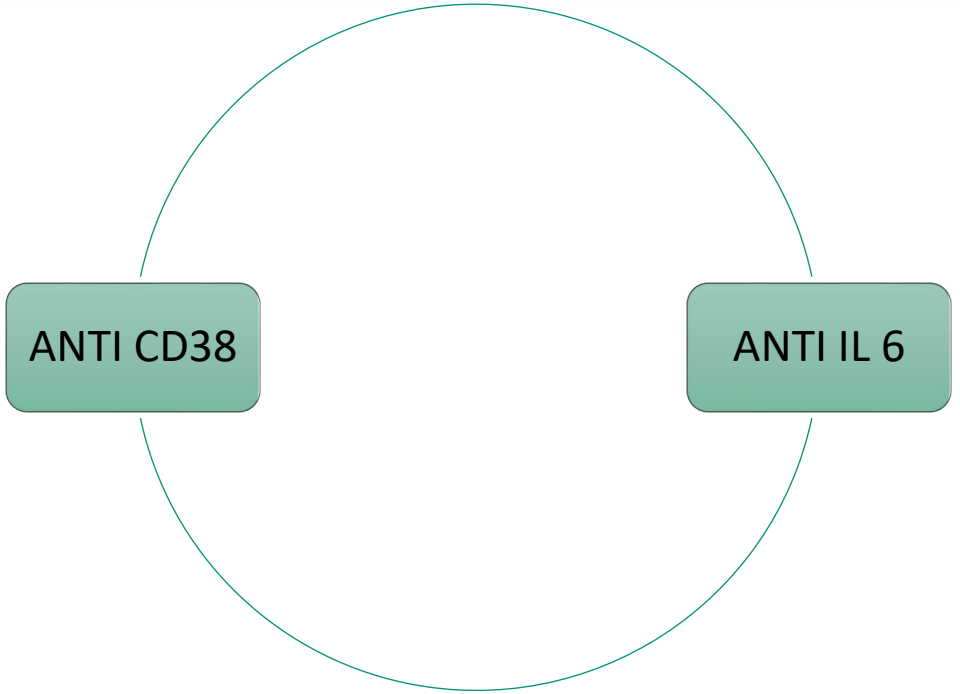
Ashley Vo

Type: Rapid Fire Oral Abstract Session

CARFILZOMIB (1)

DARATUMUMAB (2)

ISATUXIMAB (1)



TOZILIZUMAB (1)

DESENSIBILIZACIÓN

Impact of Carfilzomib and Belatacept Desensitization in Kidney Transplant Candidates With ≥ 98 - 99.9% PRA:

Early Results of ITN089ST (ADAPT) Prospective Clinical Trial

A.M. Jackson[1], K. Williams[1]

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CARFILZOMIB

Study Objectives (total enrollment = 15 subjects)

1. To assess the **safety & efficacy** of combined c

N= 5. (PHASE II, ADAPT) (CARFI + BELA).
REBOTE & CEL PLASMÁTICAS

Summary of Early Results ADAPT (N=5 subjects)

- Acceptable Safety profile
- Substantial **reductions of plasma cell subsets A & B, but not D** (long lived)
- Substantial **MFI reductions of HLA antibodies** with limited HLA antibody elimination
- **Rebound of High MFI HLA antibodies** immediately after CFZ cycle 1 observed in 3 subjects
- **Continued decay of HLA antibodies** seen > 40 weeks post treatment initiation

DESENSIBILIZACIÓN

Daratumumab (Anti-CD38) For Desensitization of Treatment-Resistant Highly HLA Sensitized ESRD Patients

Cedars Sinai

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A. Vo PharmD

DARATUMUMAB **(ANTI CD-38, PLASMATIC CELLS)**

N=7, NO SAES, NO REJECTION, DESCENSO DE MFI.

Conclusions

- Here we found Daratumumab reduced HLA CII antibody specificities.
- Daratumumab treatment also reduced DSA MFI strength and allowed for HLAi transplantation in 4 of 7 patients.
- Daratumumab was safe.

A2 A74

DESENSIBILIZACIÓN

Impact of Anti-CD38 Mab (Daratumumab) Plus Belatacept on HLA Antibodies and Bone Marrow Plasma Cells in Kidney Transplant Candidates with 100% CPRA: Early Results of ATTAIN (ITN090ST)

S. Chandran

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DARATUMUMAB **(ANTI CD-38, PLASMATIC CELLS)**

N= 15. (ATTAIN) PHASE ½ TRIAL (DARA + BELA).
REBOTE & CEL PLASMÁTICAS

Conclusions

- Combination of daratumumab and belatacept was safe and well tolerated in highly sensitized kidney transplant candidates
- Combination of daratumumab and belatacept appears to be effective in reducing HLA antibodies
  - dual antagonism of plasma cells and germinal centers
- Strategies to improve efficacy of the regimen in cohort 2
  - Increase the dose of daratumumab (8 mg/kg →16 mg/kg) to improve PC depletion
  - Additional doses of belatacept to mitigate late rebound seen in few subjects

DESENSIBILIZACIÓN

Impact of Desensitization Therapy With Isatuximab on Circulating HLA-specific Memory B Cells In Highly Sensitized Patients Waitlisted for Kidney Transplantation

Multicenter Int Clinical Trial (NCT04294459)

O. Bestard[1]

Vall d'Hebron
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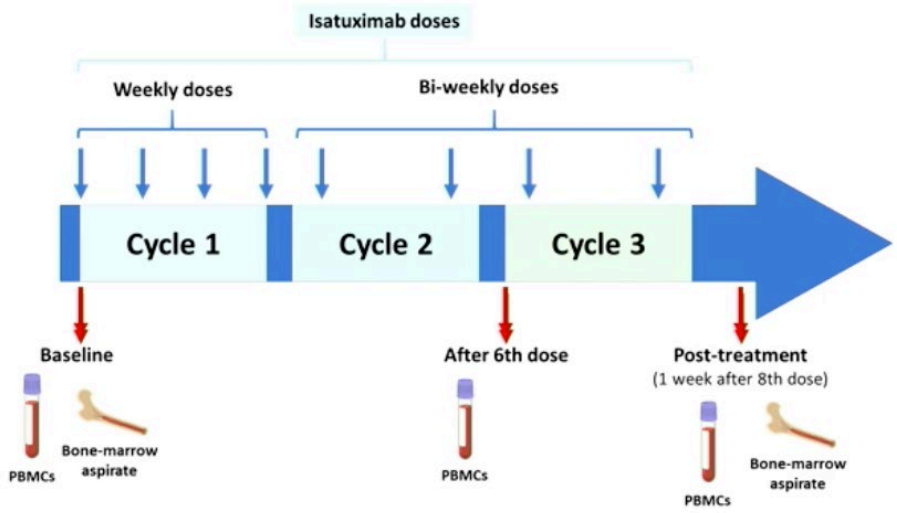
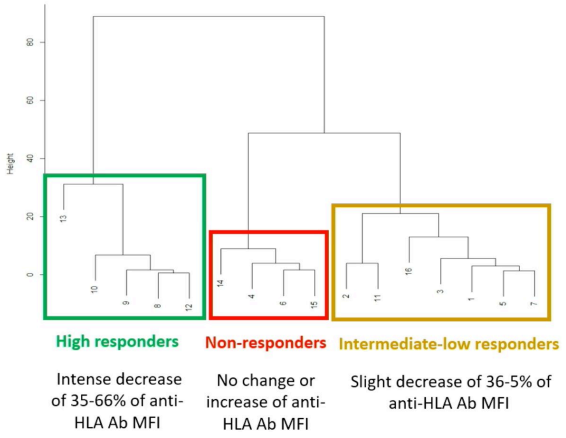
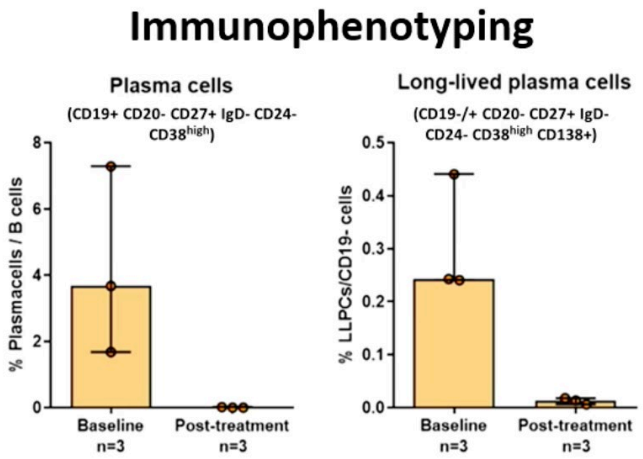
ISATUXIMAB

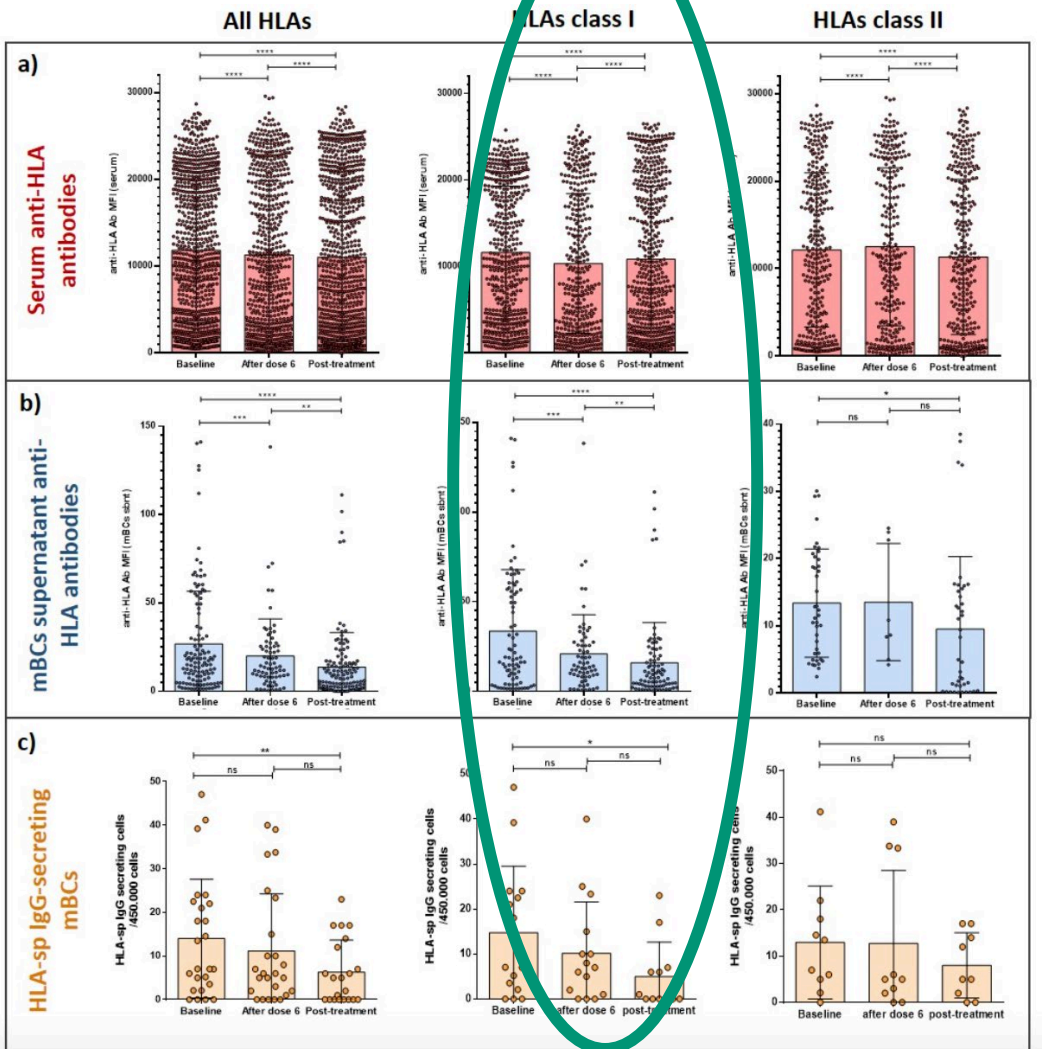
(ANTI CD-38, PLASMATIC CELLS)

8/23. REDUCCIÓN DE MFI (CLASE I) Y DE C B MEMORIA.









DESENSIBILIZACIÓN

Impact Of Tocilizumab Based Desensitization On Access To Kidney Transplantation And Outcomes After Transplantation

I. Moinuddin, MD; D. Kumar,

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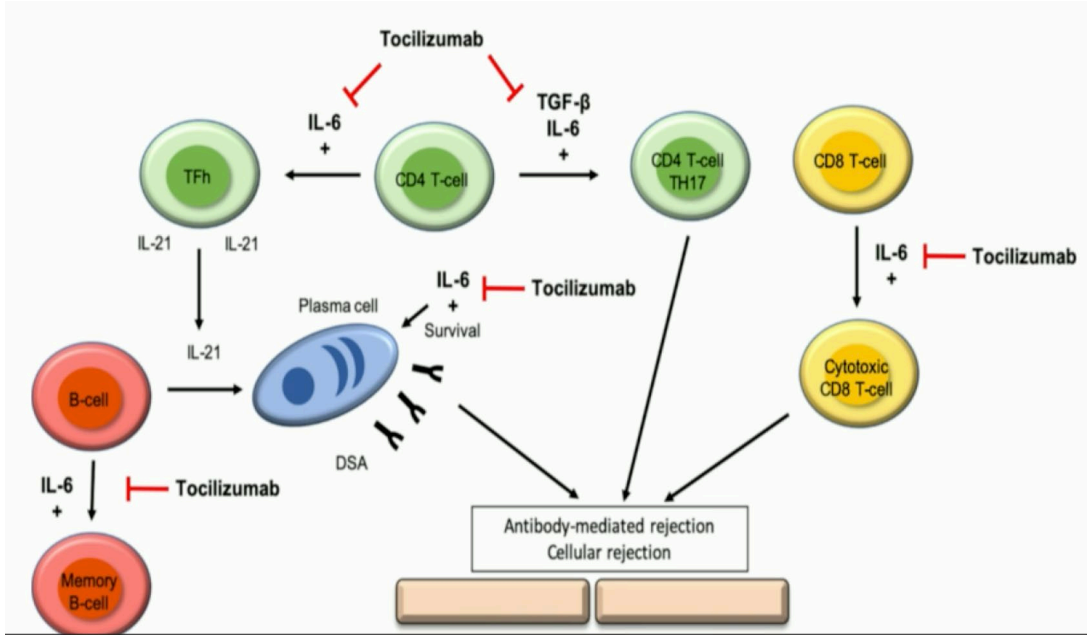
TOZILIZUMAB

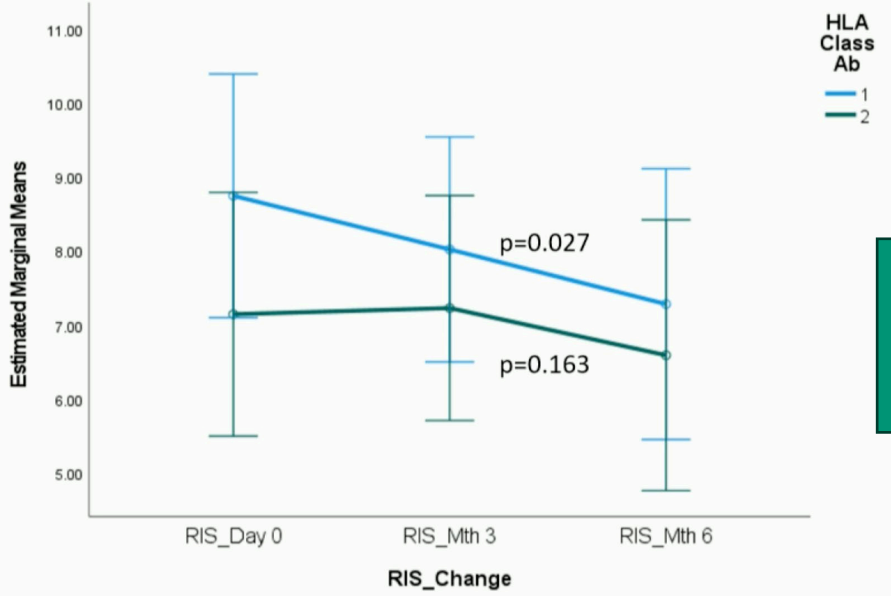
N=15,(SINGLE CENTER). 11 ACABAN, 7 TX. NO SAES, 2 SUBC REJECTION (1LOST), DESCENSO DE MFI.



Desensitization Protocol:

- Intravenous immune-globulin (IVIg) 2 gm/kg once a month for 6 doses
- Tocilizumab 8 mg/kg once a month for 6 doses.

	Pre Treatment PRA (median)	Post treatment PRA (median)	p-value
All Patients			
Class I	94%	82%	0.01
Class II	93%	73%	0.10



PERIODO DE SEGUIMIENTO SÓLO 6 MESES

NOVEDADES EN INMUNOSUPRESIÓN

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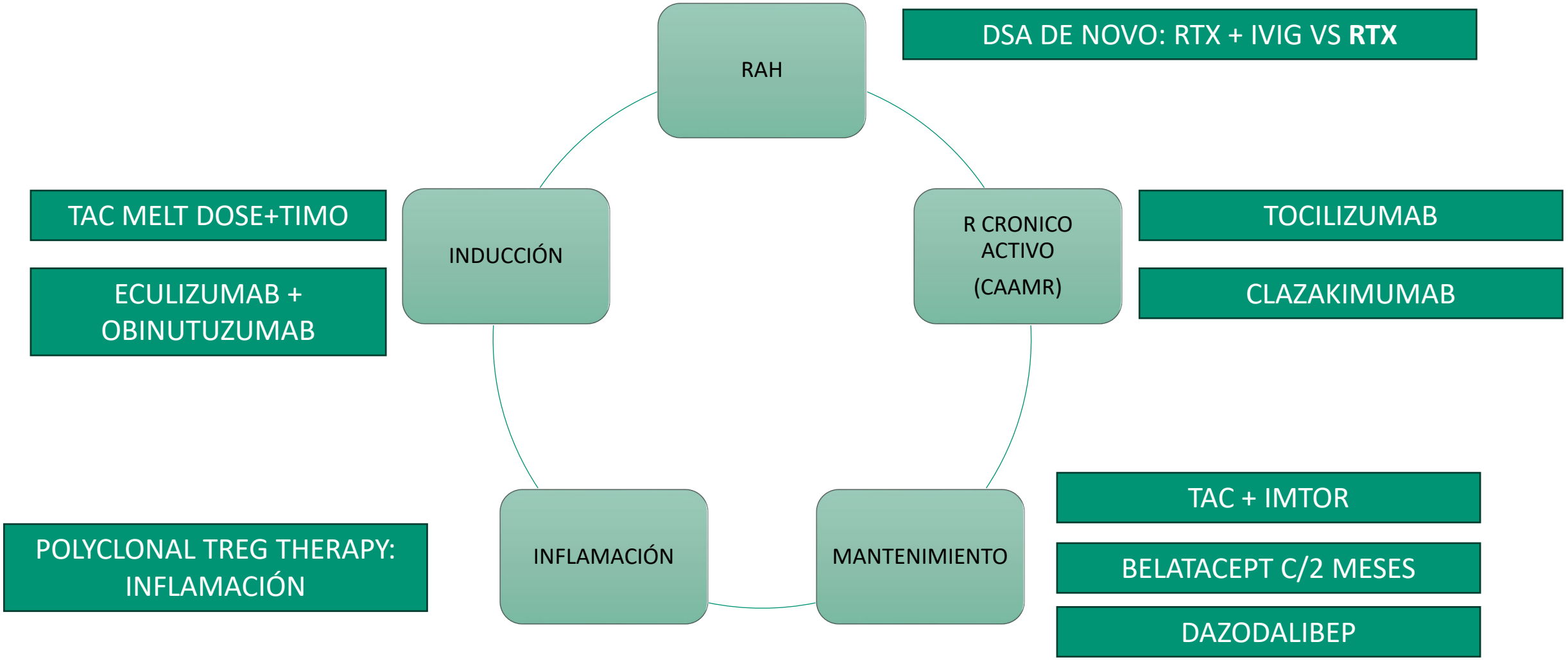

NOVEDADES EN INMUNOSUPRESIÓN

Comparison of preemptive therapy using high-dose IVIG and rituximab versus rituximab alone in kidney transplant patients with subclinical *de novo* donor-specific antibodies : a randomized clinical trial

U Gene Lee, Hyung Woo kim,
Yonsei University College of Medicine, Seoul, Korea

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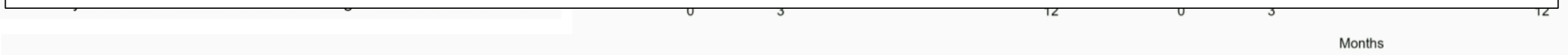
RECHAZO HUMORAL

RTX + IVIG VS RTX

N=46,(RANDOMIZED TRIAL). IVIG + RTXB NO MÁS EFECTIVO QUE RTXB SOLO

*Conclusions: **Preemptive treatment with high-dose IVIG combined with rituximab did not show a better dnDSA reduction compared with rituximab alone** for subclinical dnDSA in kidney transplant patients, although both treatments reduced dnDSA.



- No antibody-mediated rejection occurred in either group during the study

NOVEDADAES EN INMUNOSUPRESIÓN

Tocilizumab Use In Chronic Active Antibody Mediated Rejection (CAAMR): Mitigating Risks With Surveillance Donor Derived Cell Free Dna And Low Dose Strategy

S. Anand

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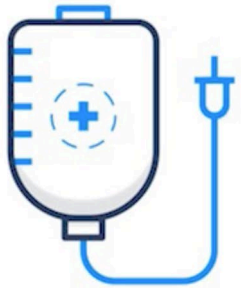
RECHAZO CRÓNICO ACTIVO

TOCILIZUMAB

N=25,(SINGLE CENTER). 2 GRAF LOST. ESTABILIZACIÓN DSA Y FX RENAL. TIEMPO DE SEGUIMIENTO CORTO

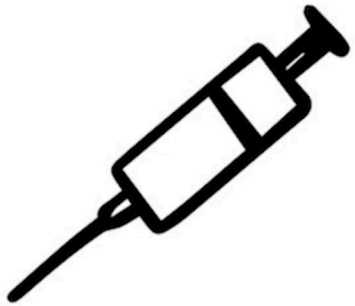
- Tocilizumab dose was 4 mg/kg intravenous monthly, with supplementation IVIG as needed, if IgG levels were low on routine monitoring

Conclusion



Tocilizumab can be safely prescribed using a low fixed dose of 4 mg/kg

patients



dd-cfDNA can monitor the response

Improved DSA, and allograft function

NOVEDADAES EN INMUNOSUPRESIÓN

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Investigator Initiated Pilot Study

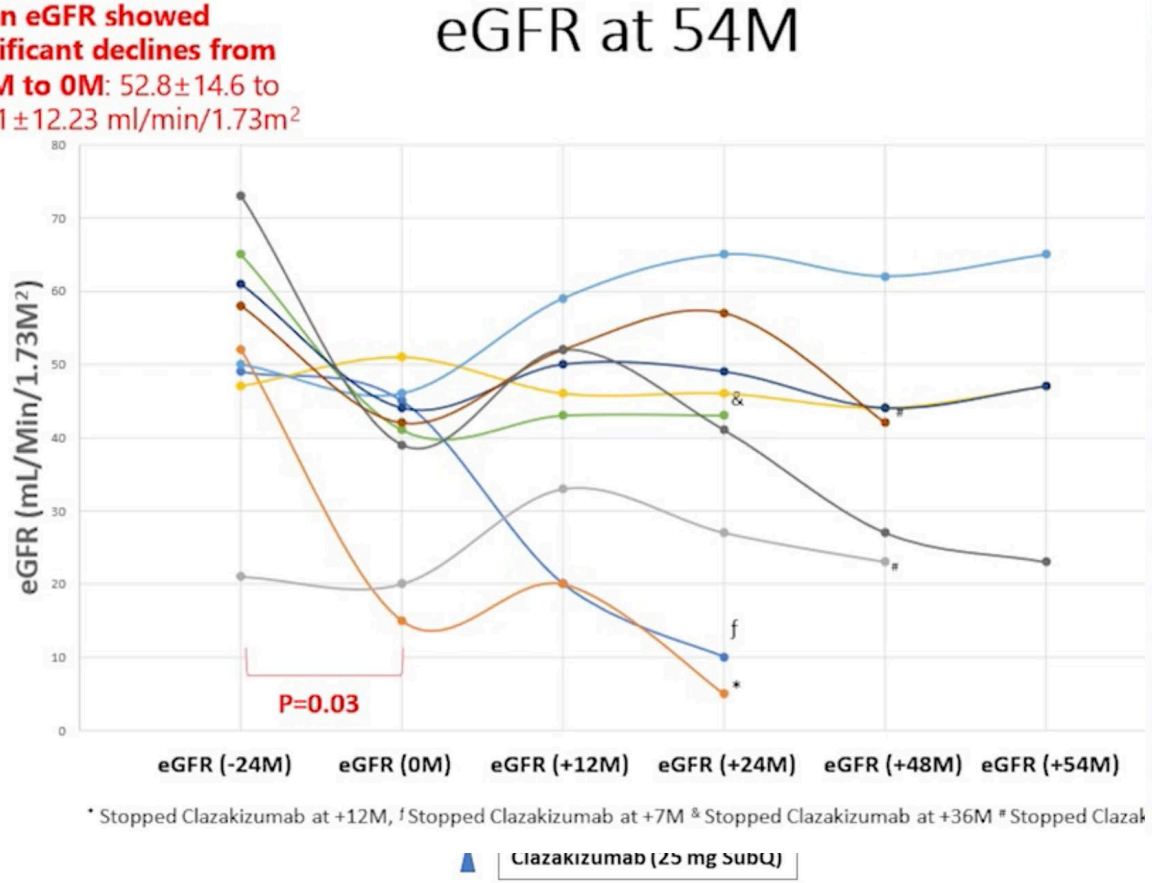
A Phase I/II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) As an Agent to Eliminate Donor Specific HLA Antibodies (DSAs) and Improve Outcomes of Patients with Chronic Active Antibody-Mediated Rejection (cABMR) Post-Kidney Transplantation: Long Term Follow Up

RECHAZO CRÓNICO ACTIVO

CLAZAKIMUMAB

N=10 (4). (PHASEI/II). ESTABILIZACIÓN DE DSA Y DE FX RENAL(5 AÑOS)
SAES (1 MUERTE). N PEQ

Mean eGFR showed significant declines from -24M to 0M: 52.8±14.6 to 38.11±12.23 ml/min/1.73m²



Serious Adverse Events, # of events (N)	Clazakizumab
SAE	**16 (6)**
Infection	
Gram negative bacteremia	1 (1)
COVID-19 infection	1 (1)
Renal	
Elevated Creatinine	3 (2)
Chronic Active antibody mediated rejection	1 (1)
Secondary FSGS	1 (1)
CNI toxicity	1 (1)
Cardiac	
Atrial fibrillation	1 (1)
Gastrointestinal	
Colitis and bowel perforation†	1 (1)
Other	
Anemia	1 (1)
Hematochezia	1 (1)
Edema left foot/left foot wound/gout	4 (1)

NOVEDADES EN INMUNOSUPRESIÓN

Five years results of de novo kidney transplant recipients treated with the combination of low dose TAC and EVE: a prospective randomized clinical trial

Patrizia Silvestri Roma

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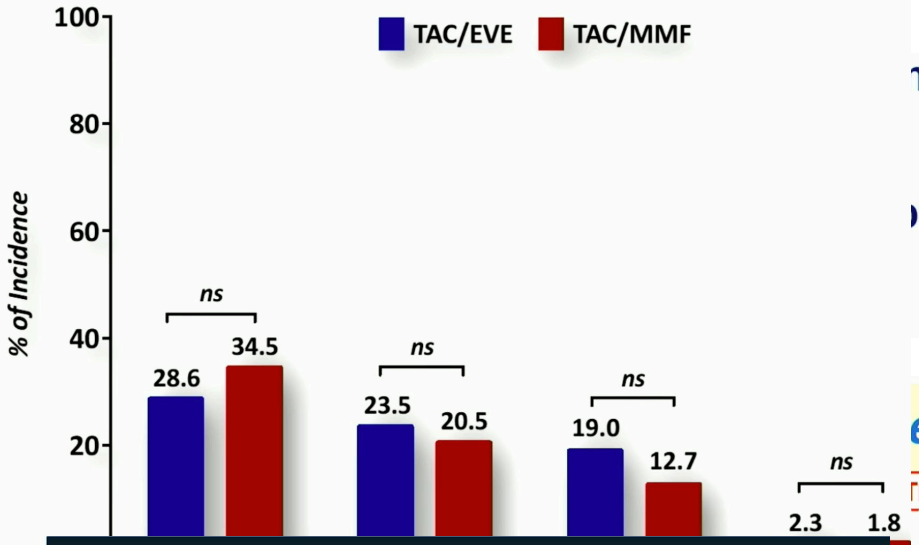
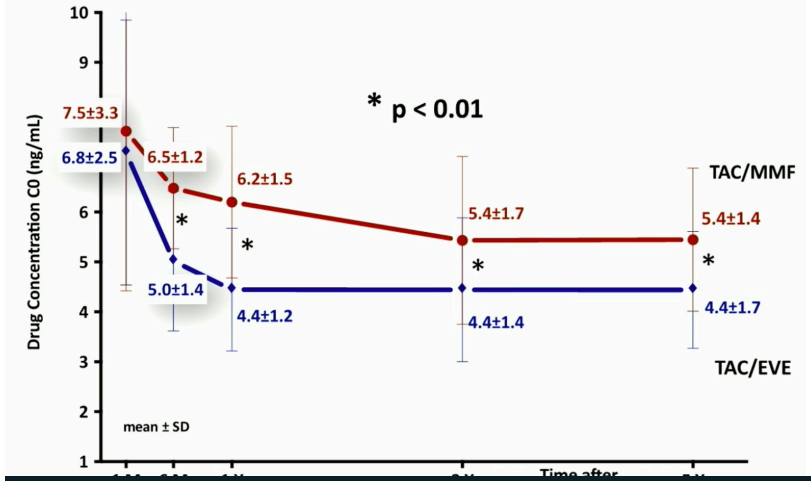
DGF, SW, Dropout, DSA



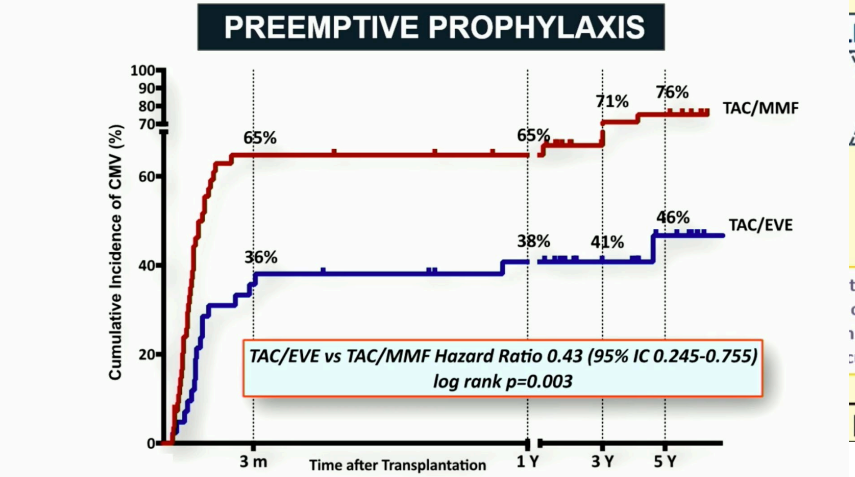
nduction and were

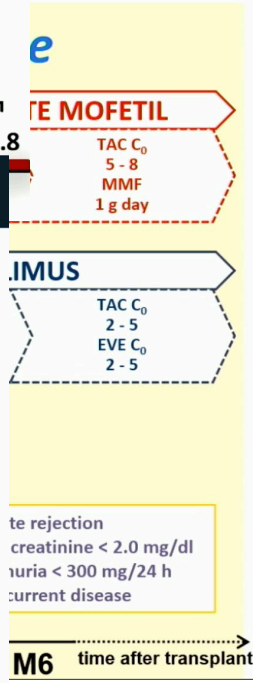
ts

Tacrolimus exposure

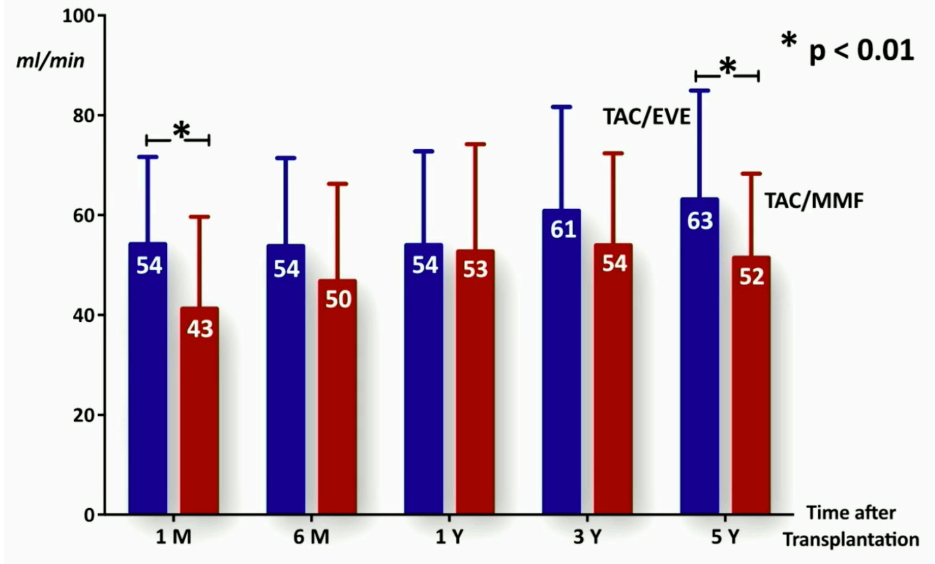


Incidence of positive PCR-DNA CMV





eGFR (MDRD)



NOVEDADES EN INMUNOSUPRESIÓN

Expanded Belatacept 2 Month Administration: Initial 6 Month Outcomes

Johanna Christensen,

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MANTENIMIENTO

BELATACEPT (C/2MESES)

Median dose of MMF 1000mg/d
Belatacept 5mg/kg monthly
Prednisone 5mg/d

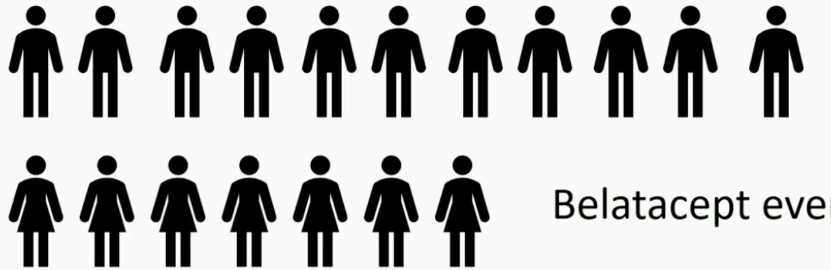
Patient Criteria

- Increased risk of infection
- Beyond 365 days from transplant
- On belatacept >1 year.
- No active infections
- No medication adherence concerns
- No history of rejection
- DSA negative, ddcfDNA <1%

N=15. (SINGLE CENTER) > 1AÑO CON BELATA, CAMBIO A C/2M. IGUAL RESULTADOS QUE MENSUAL

Conclusions:

N=15



Belatacept every 2 months

No new acute rejection
No worsening renal function

No major infectious episodes
No significant changes in immune function markers.

Potential to improve logistical and financial burdens of belatacept administration

NOVEDADES EN INMUNOSUPRESIÓN

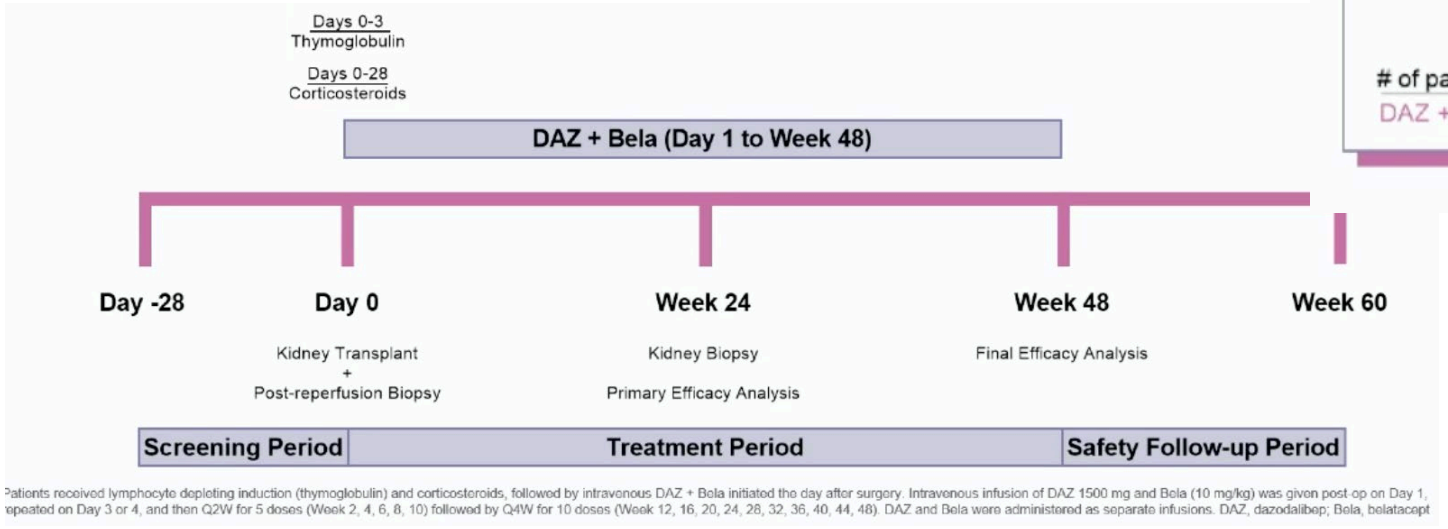
A PILOT STUDY EVALUATING DUAL CO-STIMULATION BLOCKADE WITH DAZODALIBEP AND BELATACEPT FOR PROPHYLAXIS OF KIDNEY ALLOGRAFT REJECTION (NCT04046549)

HIGHLIGHTS AMERICAN TRANSPLANT CONGRESS ATC2023 3-7, 2023

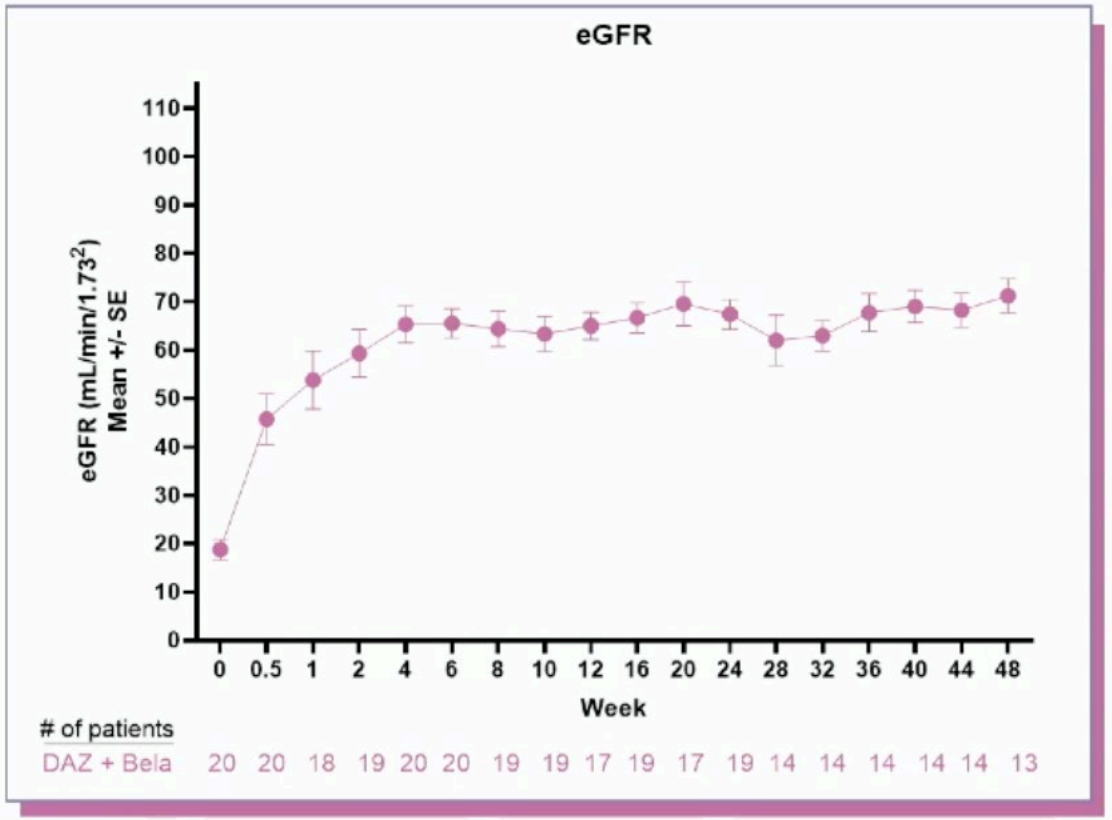
DAZODALIBEP

N=20 (12), PHASE II, SINGLE CENTER. DAZ + BELATA, 25% RA

- Dazodalibep (DAZ) is a novel non-antibody fusion protein that acts as an antagonist of CD40L
- DAZ inhibits the costimulatory signals between immune cells, including T-cells, B-cells, and antigen-presenting cells[1]



Patients received lymphocyte depleting induction (thymoglobulin) and corticosteroids, followed by intravenous DAZ + Bela initiated the day after surgery. Intravenous infusion of DAZ 1500 mg and Bela (10 mg/kg) was given post-op on Day 1, repeated on Day 3 or 4, and then Q2W for 5 doses (Week 2, 4, 6, 8, 10) followed by Q4W for 10 doses (Week 12, 16, 20, 24, 28, 32, 36, 40, 44, 48). DAZ and Bela were administered as separate infusions. DAZ, dazodalibep; Bela, belatacept



INMUNOSUPRESIÓN.

Evaluation of Extended Release and Immediate Release Tacrolimus with Early Steroid Withdrawal in De Novo Kidney Transplants Utilizing Novel Endpoints

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INDUCCIÓN

TAC MEL DOSE+TIMO+ STOP ESTEROIDES

N=117. (SINGLE CENTER) PROSP + RETROSP. INMEDIATO POST.
RESULTADOS SIMILARES TAC LCPT VS IR.

Conclusions

- LCPT when combined with rATG, MMF, and ESW is no different compared to TAC-IR with respect to the composite endpoint in kidney transplant recipients
- LCPT had statistically fewer levels <6ng/mL and more levels >14ng/mL with lower apparent clearance
- CYP3A5 was a significant factor affecting apparent clearance for both formulations

Multimodality Induction with Eculizumab and Obinutuzumab in Highly-Sensitized Deceased Donor Kidney Transplant Recipients: A Pilot Study

Evaldo Favi, Milan

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CONCLUSIONS

- Eculizumab + Obinutuzumab reduces the incidence of AMR and allograft loss
- Eculizumab prevents AMR due to persistently elevated p-DSA
- Obinutuzumab prevents AMR due to rebound p-DSA and dn-DSA
- Eculizumab + Obinutuzumab does not increase the risk of severe complications

NOVEDADES EN INMUNOSUPRESIÓN

Treg Modulation with CD28 and IL-6 Receptor Antagonists in Kidney Transplant Recipients: Results of CTOT-24, a Prospective Clinical Trial

S. Chandran, Q. Tang, J. Leung, B. Armstrong, J. Friedewald, A. Kirk, M. Morsheimer, F. Vincenti

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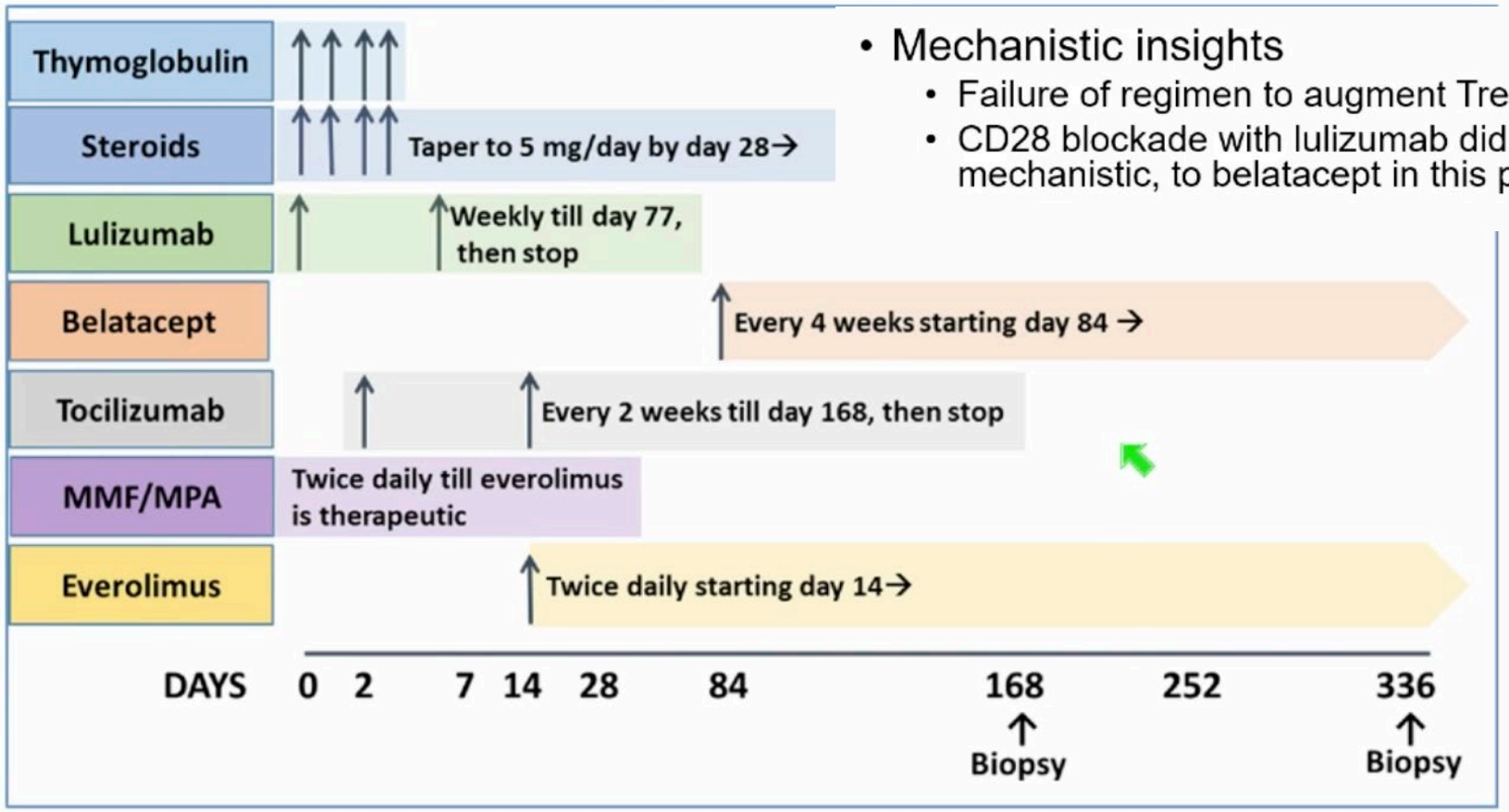
INFLAMACIÓN

MODULACIÓN T REGS (LULI)

N=(15) 8 (3). (MULTI CENTER) PILOT, SINGLE ARM. 3/5 RECHAZO. LEUCOPENIA

Selective decrease of tTregs while on lulizumab + TCZ ;



- Mechanistic insights
  - Failure of regimen to augment Tregs may underlie suboptimal efficacy
  - CD28 blockade with lulizumab did not appear to have clear advantages, clinical or mechanistic, to belatacept in this pilot study

NO ÚTIL DE MOMENTO

BIOMARCADORES

Rapid Fire Oral Abstract Session - Biomarkers

4:15PM-5:30PM Jun 3 (Pacific) Ballroom 6F Upper Level

IMPACT - Emerging Tools to Improve Defining and Managing T Cell Mediated Rejection

10:25AM-11:25AM Jun 6 (Pacific)

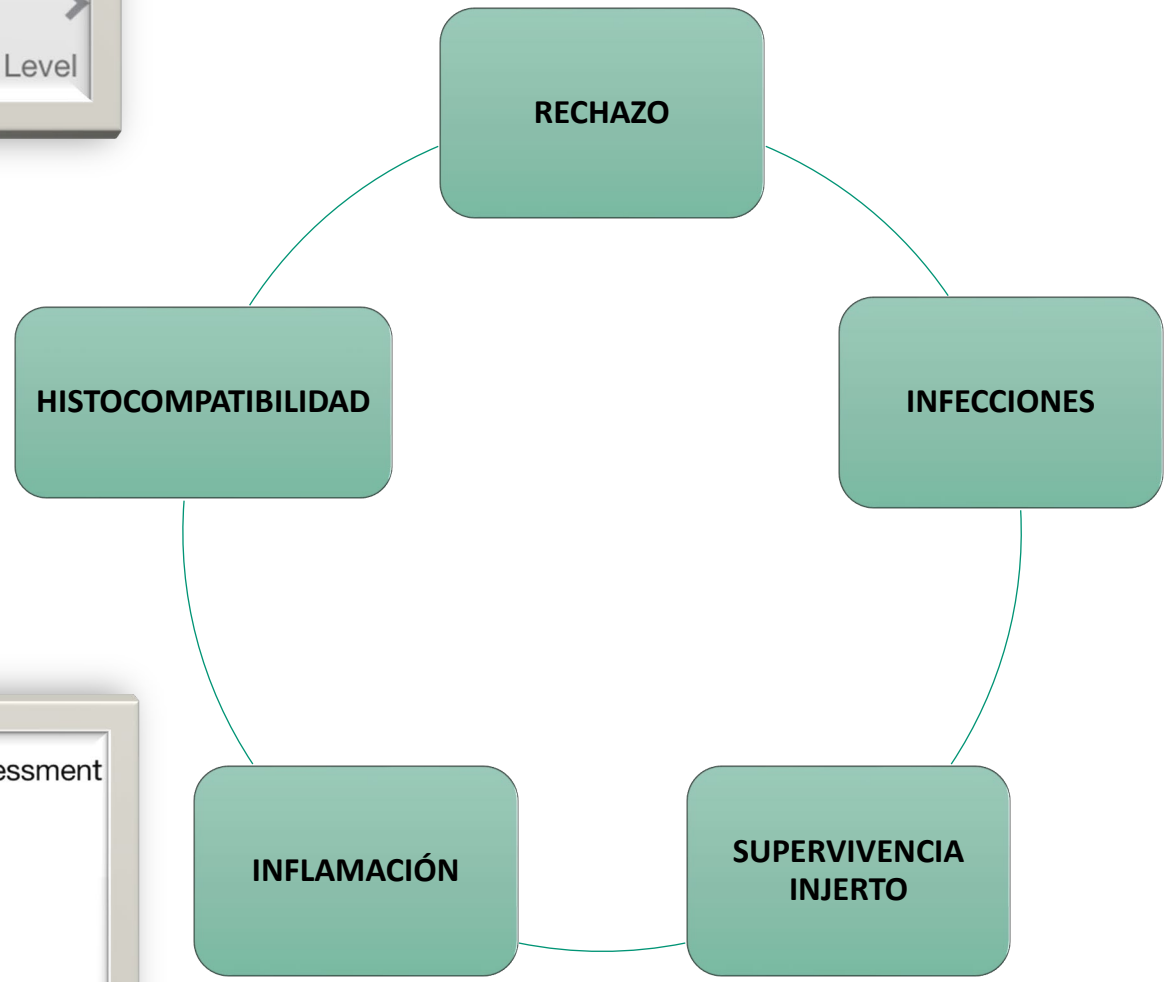
IMPACT - Monitoring Rejection and Tolerance Through High Throughput TcR Sequencing

2:00PM-3:00PM Jun 6 (Pacific)

IMPACT - Progress in the Application of HLA Epitope Data to Improve Post-Transplant Risk Assessment

7:00AM-8:00AM Jun 6 (Pacific)

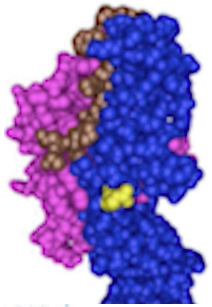
IMPACT - Target Testing to Ensure Successful Desensitization and Post-Transplant Monitoring



Predicted Indirectly Recognizable HLA Epitopes: Association with Immune Events and Modification by Immunosuppression Regimen

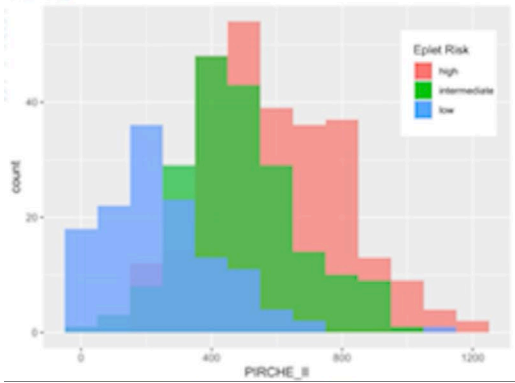
HISTOCOMPATIBILIDAD.

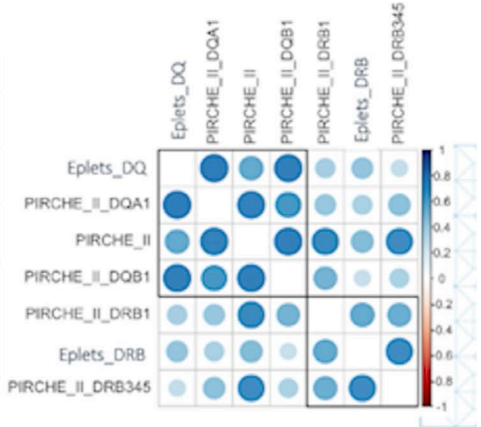
Defining genomic differences based on donor/recipient HLA alleles



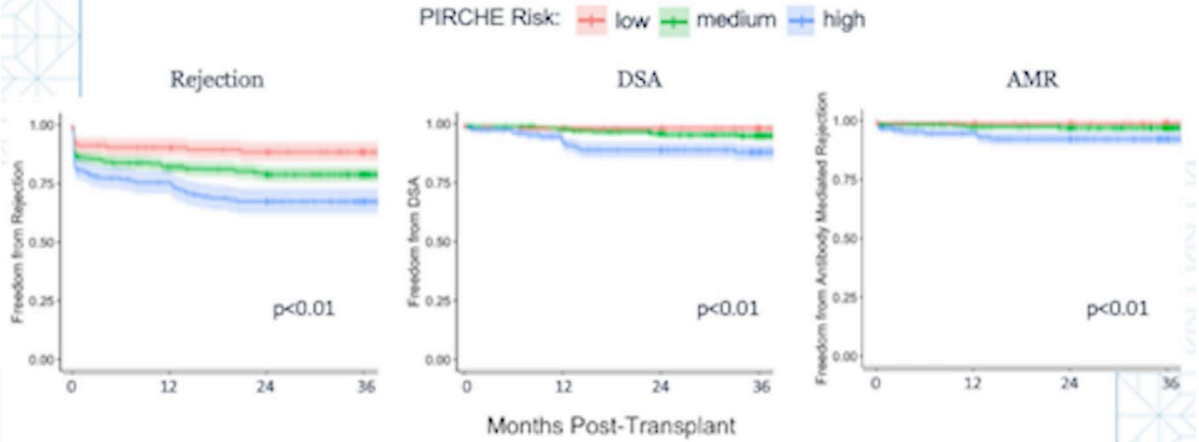
Responder		Epitope
B Cell	→	Eplets
T Cell	→	PIRCHE II

Eplet and PIRCHE scores are correlated





Effective Stratification of Immune Events



Summary

- PIRCHE-II stratifies risk of immune events
- Belatacept may moderate this effect
- PIRCHE and eplet scores are correlated
- However, both scores remain independently significant

BIOMARCADORES. B CELLS, T REGS, CD28+CD8+ T CELLS & REJECTION

RECHAZO. CITOMERTÍA DE FLUJO

Hypothesis

Kidney graft rejection may be linked to an imbalance between effector/memory and regulatory immune cells.

METHODS

1095 biopsies (Banff 2017) + lymphocyte phenotyping (flow cytometry)

Group 1 (n=802)	Group 2 (n=56)	Group 3 (n=148)	Group 4 (n=33)	Group 5 (n=56)
Normal/subnormal IFTA grade 1	**IFTA** grade 2 or 3	**ABMR**	**TCMR**	**Borderline** rejection

Rejection of all types

ABMR & TCMR are associated with a decrease in the ratio of B cells/CD28-CD8+ T cells

The ratio of B cells/CD28-CD8+ T cells is 55% higher in patients with normal biopsies compared to those with ABMR.

Rejection of all types is associated with an increase in the ratio of CD28-CD8+ T cells/Tregs

BIOMARCADORES.

A composite model allowing noninvasive diagnosis of subclinical rejection at one year after kidney transplantation

Danger R. *et al.*, Kid Int. 2023

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JUNIO 3-7, 2023

RECHAZO

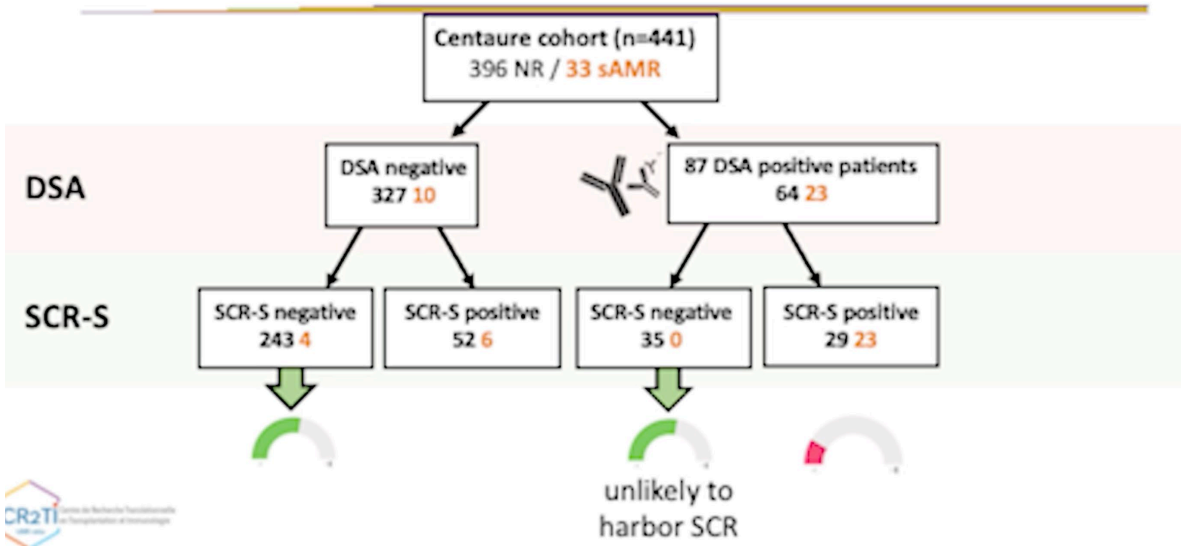
MODELO QUE INCLUYE ESTUDIO GENÉTICO EN SANGRE +INFORMACIÓN CLÍNICA PREDICE subclin AMR

A retrospective and multicentric study

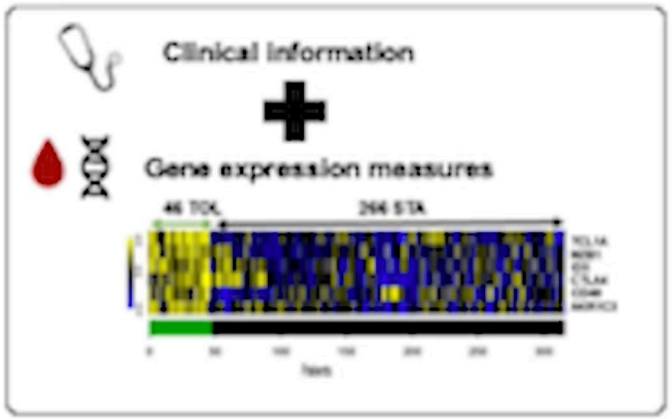
588 kidney transplanted patients and paired biopsies and blood samples at one-year post transplantation

from 3 French centers: Lyon, Paris Necker and Nantes

Reclassification of antibody mediated subclinical rejection (sAMR)

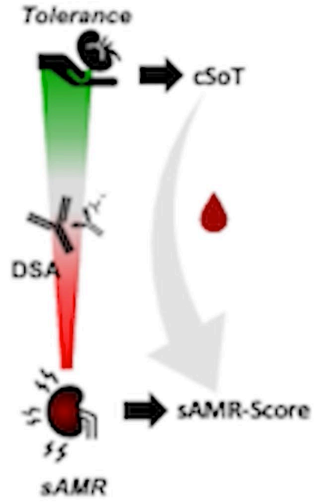


composite Score of Tolerance (cSoT)



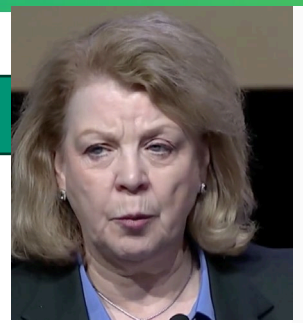
- Validation of our hypothesis:
  blood expression of tolerance-associated genes is associated with DSA and SCR diagnosis
- Improvement of a SCR composite score with only 2 genes
  High NPV values
  Using different methods for gene expression measure

➡ Proposed as an non-invasive aid for SCR diagnosis
May improve DSA stratification



BIOMARCADORES

RECHAZO. IA



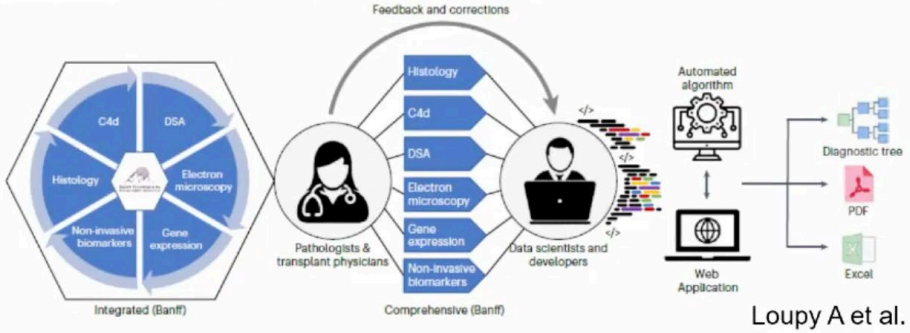
Towards an Improved Diagnostic Standard for Kidney Transplant Rejection: Reflections on the Banff Classification and Precision Medicine Approaches

Roslyn B Mannon, MD, FAST, FASN

APLICACIÓN DE INTELIGENCIA ARTIFICIAL EN HISTOLOGÍA

Steps to Development of the Comprehensive Banff Automation System

- Development involves multidisciplinary approach
- Imported all Banff rules and NLP of reports
- Decoding, encoding and rectifying processes
- Outputs are decision trees and automated reports
- 4409 biopsies from 3054 patients from 20 Tx centers in EU and NA
  56% surveillance/44% indication bx



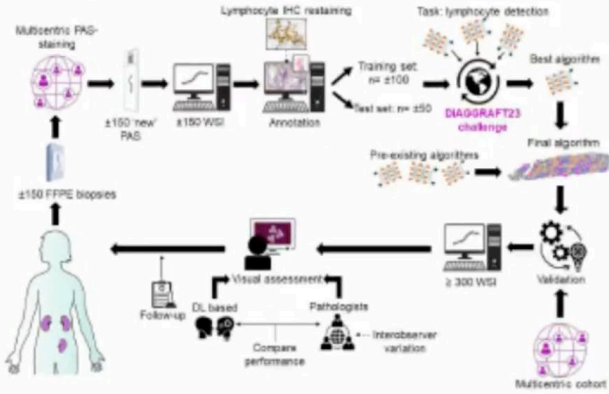
NCT05306795

Loupy A et al. *Nat Med* 2023 in press

Banff Digital Pathology Working Group

Am J Transplant. 2020.
PMID: 32185875.

Radboudumc Diagnostic Image Analysis Group/ **DIAGGRAFT Study**



https://www.computationalpathologygroup.eu/projects/diaggraft/

BIOMARCADORES.
Secuenciación de alto rendimiento de receptores de C T

HIGHLIGHTS
AMERICAN TRANSPLANT CONGRESS
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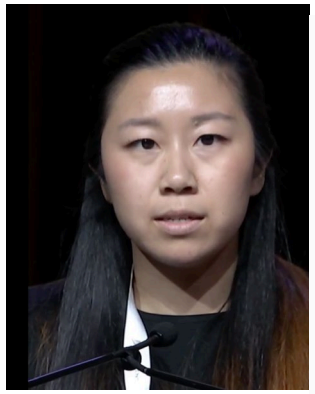


Benefits of Single-Cell Technologies

Pros:
- Linking gene expression to individual cells
- Understanding of heterogenous cell populations
- TCRαβ clonal analysis
- Integration of multi-omic analysis

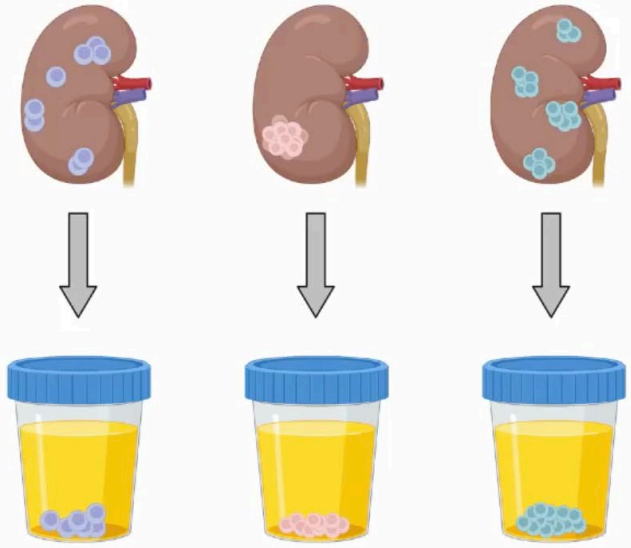
Cons:
- $$$
- Time-intensive & more difficult to analyze
- Challenge of tissue dissociation
- Limited # of cells

Brings into question…

- Are endpoints for anti-rejection therapies adequate?
- What is the specificity, phenotype, and function of persisting $CD8_{EXP}$?
- Could persisting $CD8_{EXP}$ be associated with subsequent rejection? Or tolerance?

CARO PERO ÚTIL?

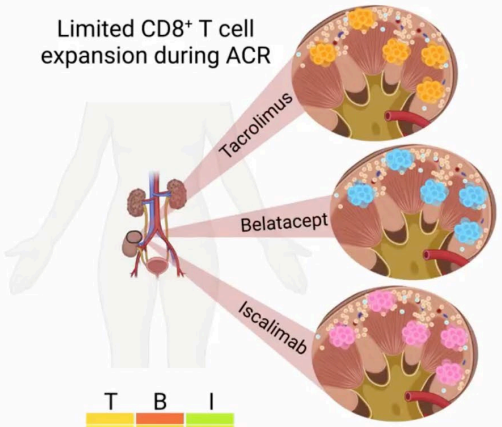
Urine as a surrogate biopsy?

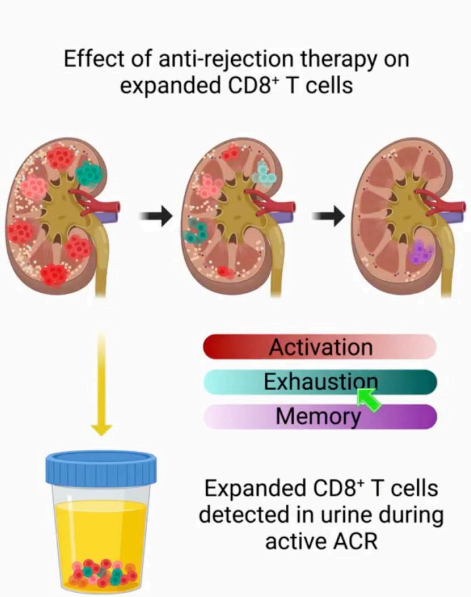


Do $CD8_{EXP}$ in the urine maintain their phenotype and gene expression profile?

A simple pathway analysis of $CD8_{EXP}$ in urine could inform therapeutic choice

The power of graft-derived TCRseq





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Non-invasive Diagnosis of Rejections in Urine by Monitoring Donor Reactive T Cell Clones

HIGHLIGHTS
AMERICAN TRANSPLANT CONGRESS
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RECHAZO. SECUENCIACIÓN GENÉTICA ALTO RENDIMIENTO

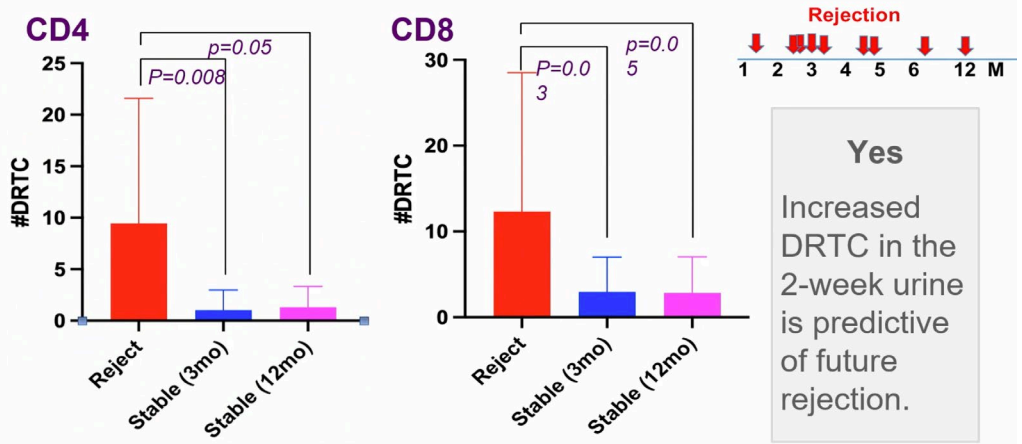
Monitoring for DRTCs can be used as a potential diagnostic/predictive tool and that this can be achieved non-invasively through analysis of urine.

Prospective Study in Kidney Transplant Recipients to test if Donor-Reactive T Cell (DRTC) Repertoire can Diagnosis / Prediction of Rejection (n=80)

Hypotheses tested:

- Increased DRTC in biopsies is diagnostic of rejection
- Diagnosis of rejection can be done non-invasively in blood and urine.
- Increase in DRTC in blood and urine can predict an upcoming rejection.

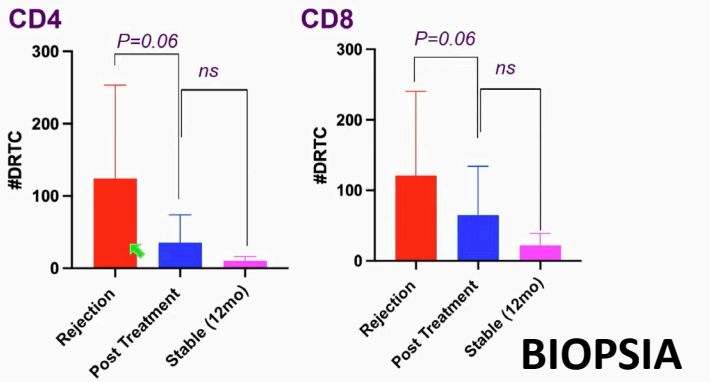
Can TCR-AlloSEQ Predict Rejection from 2-week urine?



Yes

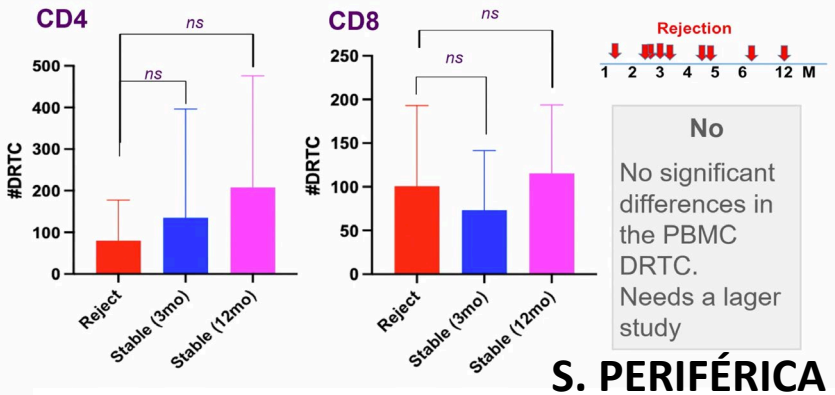
Increased DRTC in the 2-week urine is predictive of future rejection.

Do DRTC in Allograft Change with Treatment?



BIOPSIA

Can TCR-AlloSEQ Diagnose Rejection in PBMC?

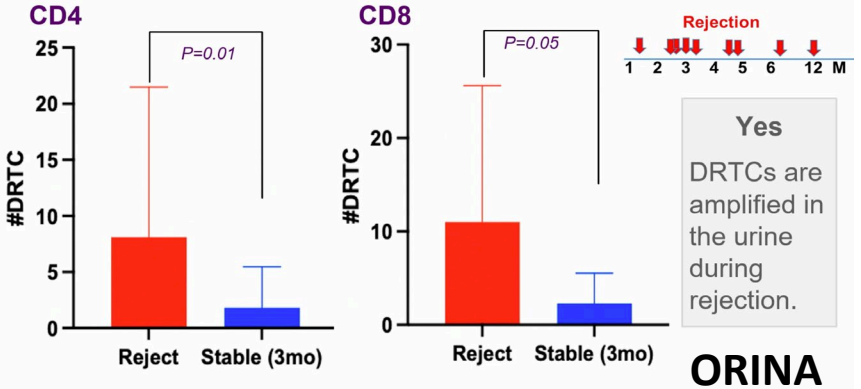


No

No significant differences in the PBMC DRTC. Needs a lager study

S. PERIFÉRICA

Can TCR-AlloSEQ Diagnose Rejection in Urine?

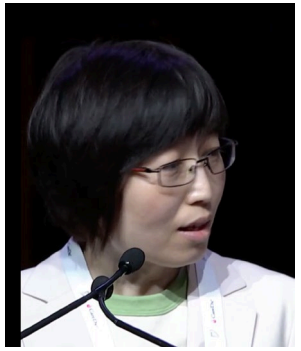


Yes

DRTCs are amplified in the urine during rejection.

ORINA

TOLERANCIA. SECUENCIACIÓN GENÉTICA DE ALTO RENDIMIENTO



Monitoring Tolerance Through High Throughput TCR Sequencing

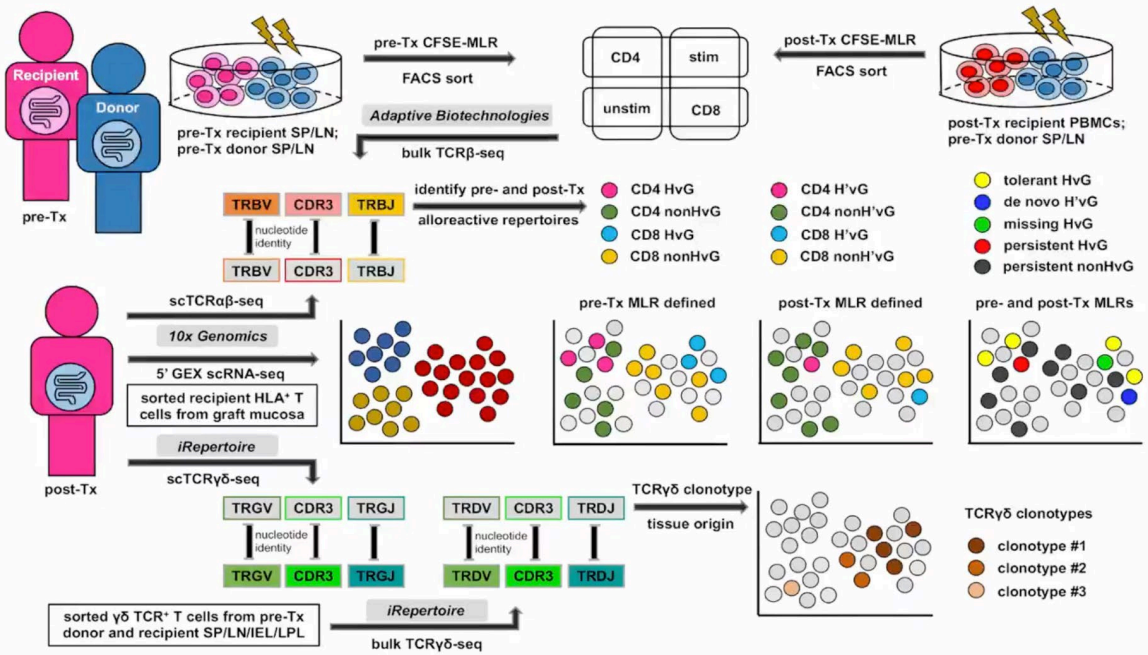
Question

Regulation followed by **deletion of donor-specific T cells in long-term?** However, in vitro assays cannot distinguish between anergy and deletion.

Hypothesis

High throughput TCRβ CDR3 sequencing of transplant recipients' **donor-reactive T cells** prior to transplant would allow identification of clones that recognize their organ donor's alloantigens. These donor-reactive T cells could be **tracked *in vivo*** in the post-transplant period.

Ongoing applications



Bulk TCRβ-seq + scRNA-seq (5'GEX-seq + TCRαβ-seq + TCRγδ-seq) : to integrate functional gene profiles with alloreactivity and individual T cell clonotypes

- Morris et al. Sci Transl Med (2015)
- Zuber et al. Sci Immunol (2016)
- Fu et al. Cell Stem Cell (2019)
- Fu et al. J Clin Invest (2021)
- Obradovic et al. Software Impacts (2021)
- Fu et al. Frontiers in Immunology (2021)
- Fu, J., Sykes, M. Transplantation (2021)
- Long K, Fu J. STAR Protocols (2023)
- Fu J et al. under review

BIOMARCADORES.

Adapting Imaging Mass Cytometry To Explore Renal Allograft Inflammation And Develop A Tissue-based Classifier

HIGHLIGHTS
AMERICAN TRANSPLANT CONGRESS
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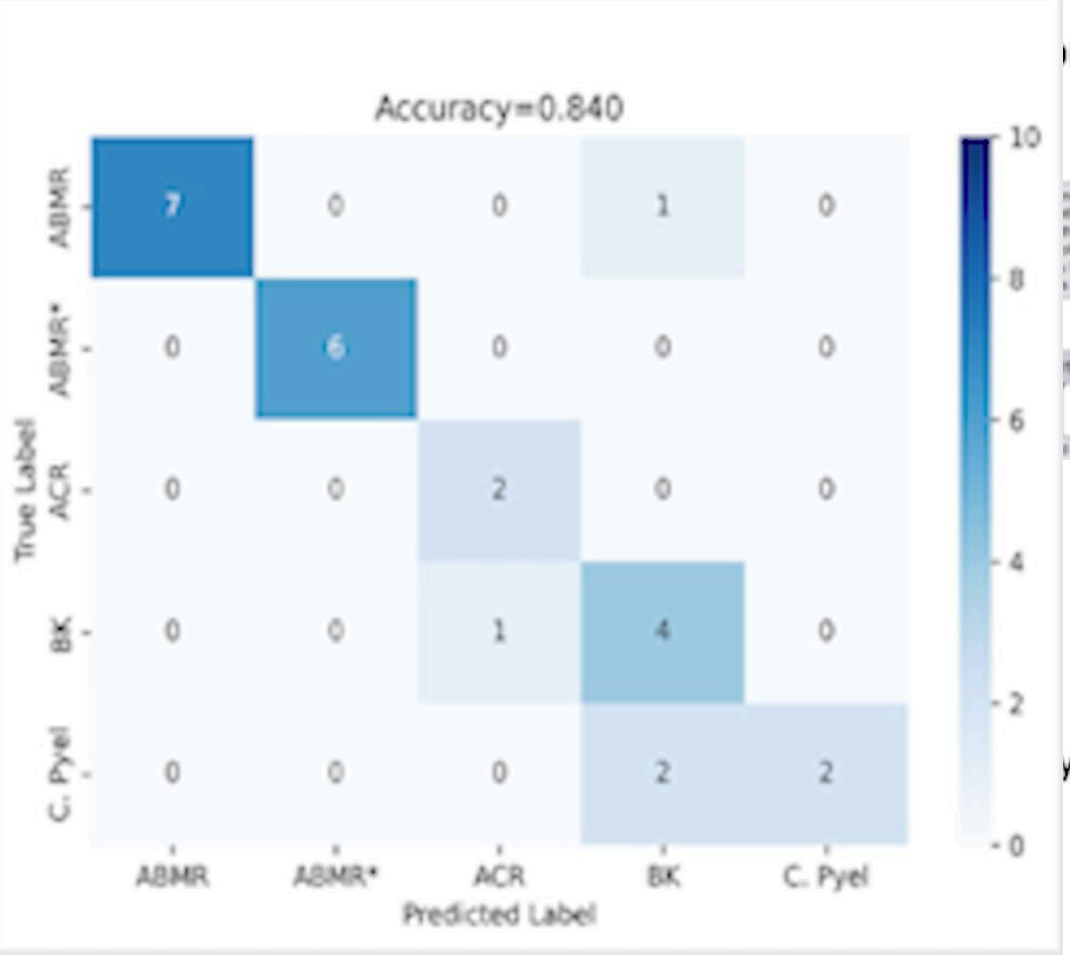
INFLAMACIÓN. ESPECTROMETRÍA DE MASAS



CONCLUSIONS

- We have established a novel, IMC-based approach to quantify & characterize immune subpopulations in renal allograft inflammation.
- We have incorporated intracellular spatial features to develop a novel classifier of allograft inflammation, demonstrating high diagnostic accuracy.

BIOMARCADORES.

"Dose-response Curves Characterization Of Immunobiogram, A Novel Immunoassay To Test The Pharmacodynamic Response To Individual Immunosuppressive Drugs In A Representative Sample Of Kidney Transplant Recipients" (IMMUNOTRANS STUDY)

INFECCIÓN/RECHAZO. INMUNOBIOGRMA

MULTICÉNTRICO. N=210. PACIENTES CON DSA RESPONDEN MENOS A A INMUNOSUPRESIÓN Y CMV O BK MÁS

Objectives

- To analyze the value dis
  each IMS tested) in a re
  transplant patients in m
- To explore the associati
  individual IMS with the

Design:

Observational and cross-
of clinical events.

Sample:

- Patients with a RT at
- Stratified sample to
  with each treatment
- Final Analysis N=210

Sample description

11 years since transplant
Minimum 50 patients wit

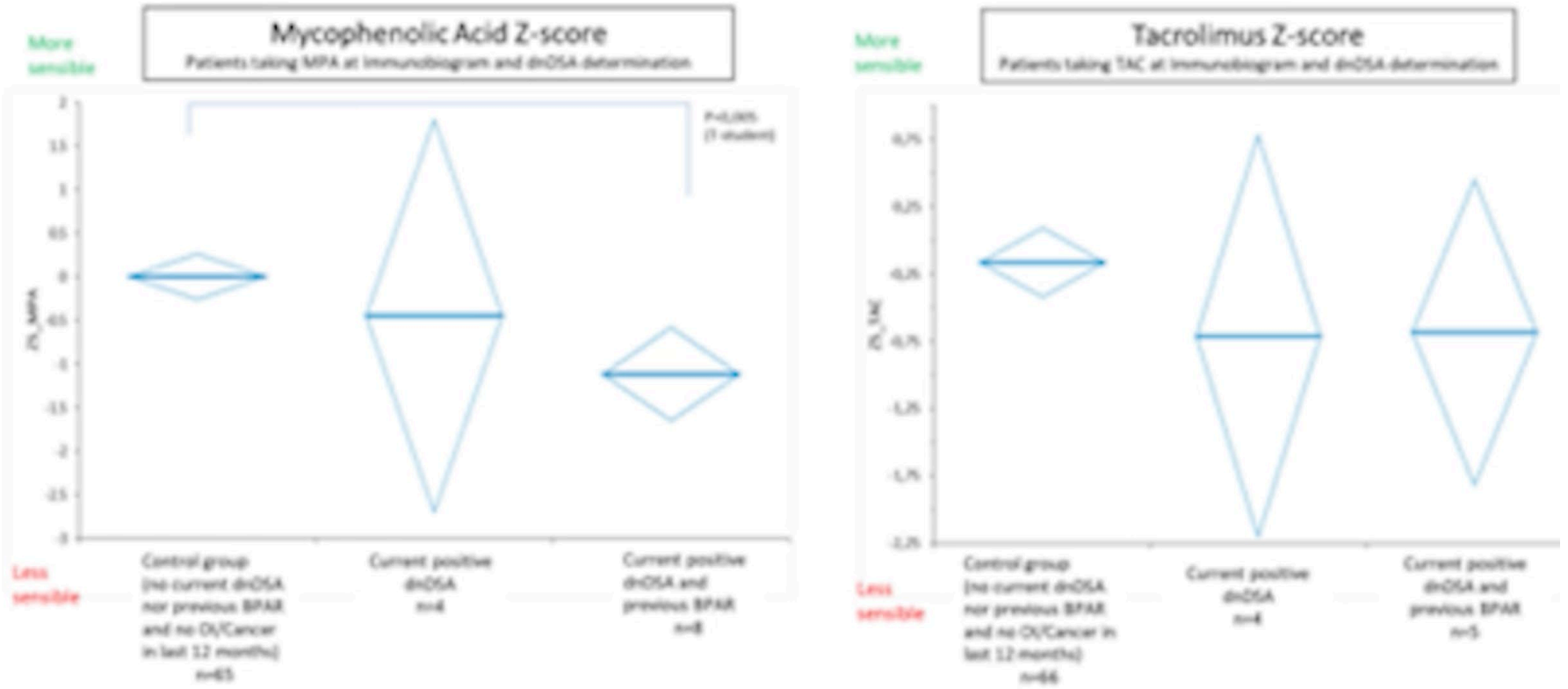


Figure 2. IMBG Z Score in subgroups of patients taking MPA or TAC

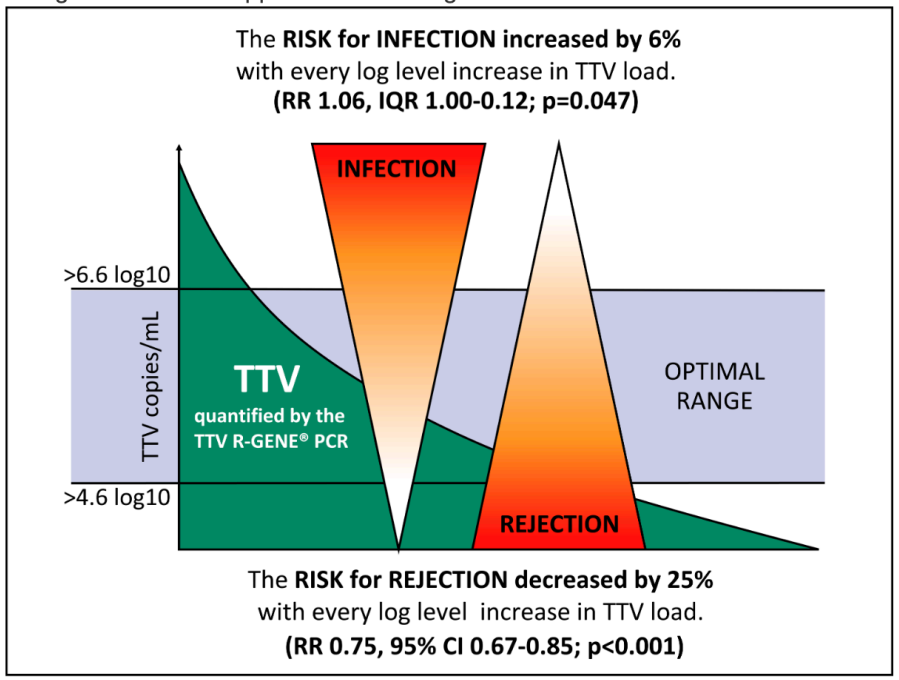
Patients with current dnDSA positive values showed a less responsive profile to the IMS than the control group

Activation Ratio showed to be lower in the group of patients clinically more immunosuppressed (with opportunistic infections due to CMV or VBK in the last 12 months) vs healthy donors

INFECCIÓN/RECHAZO. INMUNOBIOGRMA

Validation of the Optimal Torque Teno Virus Range for Risk Stratification of Graft Rejection and Infection in Kidney Transplant Recipients by a Commercial PCR

***Conclusions:** This study supports the value of TTV for risk stratification of graft rejection and infection post kidney transplantation applying a commercial PCR. The optimal TTV-range refined by these data will be applied in an interventional randomized controlled trial to assess the safety of TTV-guided immunosuppression: the TTVguideIT trial.



Next Generation Sequencing of the Microvirome in a Cohort of Renal Transplant Recipients with Unexplained Viral Syndromes

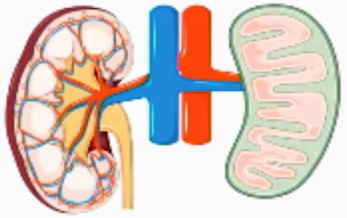
BIOMARCADORES. MITOCONDRIAS PRE TRASPLANTE & DGF

SUPERVIVENCIA INJERTO

Pre-Transplant Mitochondrial Respiration in Human Kidney Allografts Predicts Clinical Outcome Upon Transplantation

- **Biomarkers with robust predictive capacity are necessary:**
  - Donor Parameters
  - Histology
  - Cell viability – real-time confocal microscopy (Weissenbacher et al., Ann Surg, 2019)

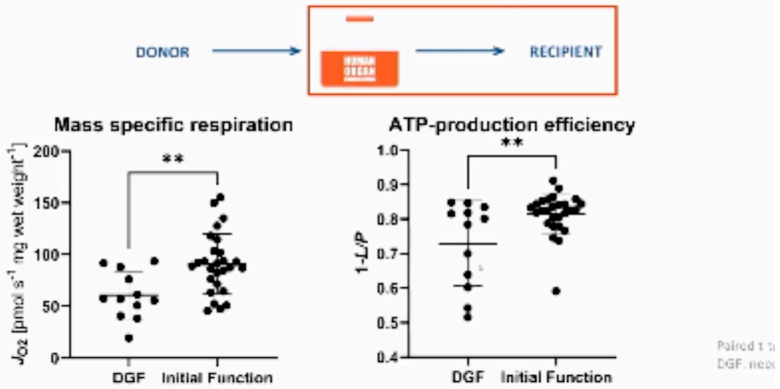
CONCLUSION



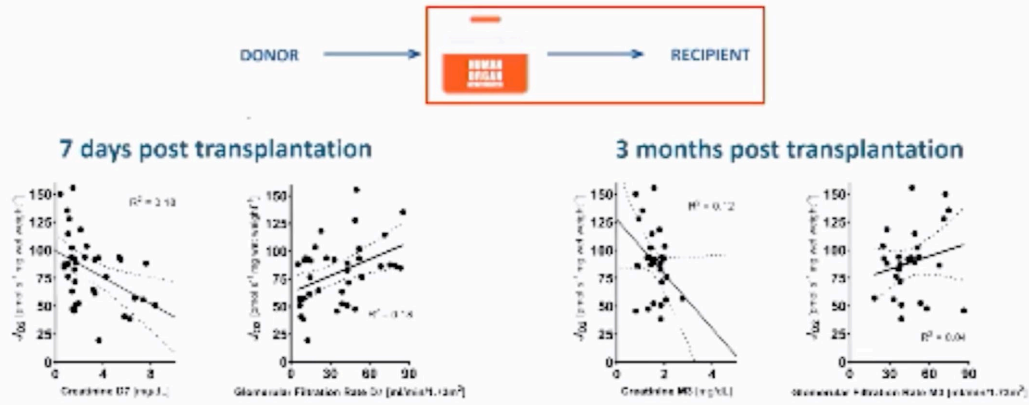
- Bioenergetic performance reflects donor conditions
- Mitochondrial respiration ATP-production efficiency → Graft performan
- Mitochondrial function predicts the outcome after transplantation

→ Evaluation of mitochondrial function is a promising assessment tool for kidney allografts

MITOCHONDRIAL RESPIRATION PREDICTS DGF

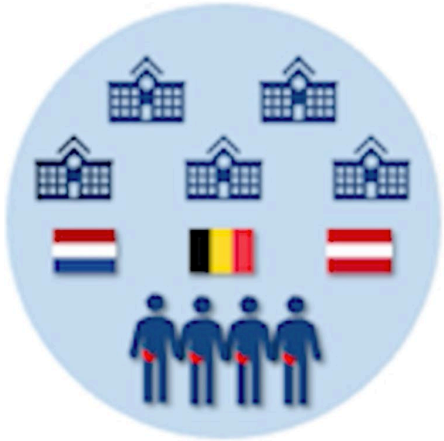


MITOCHONDRIAL RESPIRATION PREDICTS CREA AND GFR

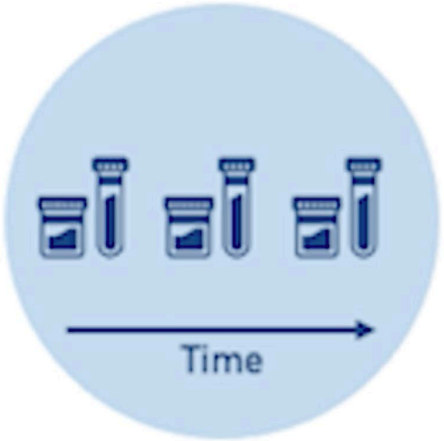


BIOMARCADORES. CREATININA Y PROTEINURIA & DCGF MODELO DE PREDICCIÓN DINÁMICO.

Development of high-performing and multicenter-validated dynamic prediction models with longitudinal measurements of serum creatinine and proteinuria for death-censored graft failure



4131 KTRs from NL, BE, AU



508.541 measurements

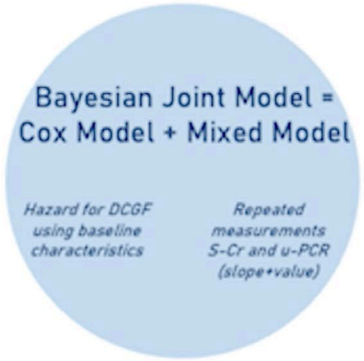
S-Cr/proteinuria

Median FU:

7 years

Outcomes of interest

Statistics



- Multicenter-validated, dynamic prediction model for DCGF with great prediction metrics
- Performance in other allocations areas pending
- Objectify allograft prognosis for physicians and patients
- Individual predictions = personalized surveillance?
- Concept of Joint models valuable for other outcomes of interest (AR, ABMR, TCMR)
- Dynamic prediction model will ultimately be made open-access for everyone

BIOMARCADORES. COMPOSICIÓN CORPORAL Y MORTALIDAD EN LISTA DE ESPERA.

Abdominal CT Measurements of Body Composition and Waitlist Mortality in Kidney Transplant Candidates

OBESIDAD Y SARCOPENIA PREDICE MORTALIDAD

Table 3: Unadjusted and Adjusted Associations between CT-based Body Composition at Kidney Transplant Evaluation and Wait List Mortality among KT Recipients in National Registry (n=828).

	Model 1* cSHR (95% CI)	Model 2§ aSHR (95% CI)
Sarcopenia		
Non-Sarcopenic	Reference	Reference
Sarcopenic	1.13 (0.82, 1.56)	0.93 (0.67, 1.31)
Myosteatosis		
Non-Myosteatosic	Reference	Reference
Myosteatosic	**1.83 (1.23, 2.71)**	**1.62 (1.07, 2.45)**
Sarcopenic Obesity		
Non-Sarcopenic Obesity	Reference	Reference
Sarcopenic Obesity	**1.62 (1.05, 2.49)**	1.42 (0.90, 2.23)

* Unadjusted

§ Adjusted for age at EV, gender, time on dialysis, and dialysis type

Conclusion

- Myosteatosis is associated with waitlist mortality when adjusted for age, gender, dialysis time and dialysis type.
- The association of myosteatosis and waitlist mortality differed by age (≥65), with younger candidates being at greater risk when having myosteatosis.
- The association of sarcopenic obesity and waitlist mortality differed by age (≥65) and frailty, with younger and frail candidates being at greater risk.

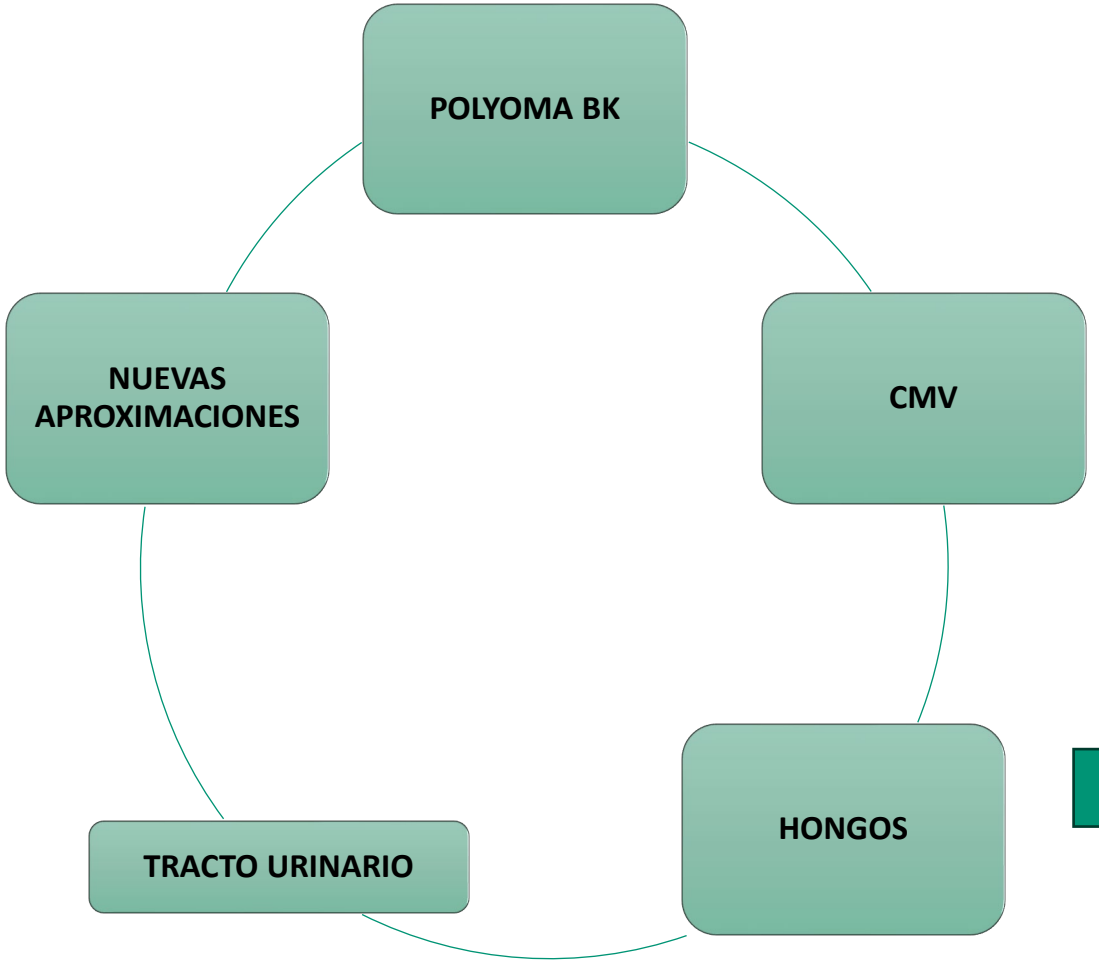
Take home message:
Existing CT measurements could be a valuable tool to improve risk stratification among kidney transplant candidates.

INFECCIONES

MAU 868

POSOLEUCEL

NUEVAS GUÍAS



CICLOS ANTIBIÓTICOS MÁS CORTOS ?

NUEVOS ANTIBIÓTICOS

MULTIRESISTENCIAS

LETERMOVIR

FIZTASOVIMAB

OLOROFIM

+ ESTUDIOS

BACTERIURIA ASINTOMÁTICA

NO TRATAR

Posoleucel as Preemptive Therapy for BKV Infection in Kidney Transplant Recipients: Safety and Tolerability in a Phase 2 Trial

Anil Chandraker[1]

HIGHLIGHTS
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POLYOMA VIRUS BK

POSOLEUCEL

PHASE II. DOBLE CIEGO N=61. BIEN TOLERADO.
EFICAZ (VIREMIA): + DOIS VS -DOSIS VS PLACEBO
3 REJECTION (NO RELACIONADO)

	PSL q14d N=20	PSL q28d N=18	PBO N=14
Pts w/ BK VL decreased by ≥1 $\log_{10}$ BKV DNA copies/mL vs baseline, n (%)	10 (50)	5 (28)	2 (14)
BK VL reduction from baseline, median $\log_{10}$ BKV DNA copies/mL (min, max)	-0.9 (-2.1, 0.1)	-0.45 (-1.8, 0.5)	-0.15 (-2.1, 0.3)
BK VL ≥50% reduction, n (%)	17 (85)*	10 (56)	6 (43)
Change in eGFR⁺, median mL/min/1.73 m^2 (min, max)	-2.5 (-11, 7)	0 (-16, 20)	0 (-21, 9)

Posoleucel antiviral response greater than placebo

	PSL q14d N=8	PSL q28d N=8	PBO N=4
Pts w/ BK VL decreased by ≥1 $\log_{10}$ BKV DNA copies/mL vs baseline, n (%)	6 (75)	5 (63)	1 (25)
BKV VL reduction, median $\log_{10}$ BKV DNA copies/mL (min, max)	-1.4 (-2.1, 0.1)	-1.5 (-1.8, -0.2)	-0.4 (-2.1, -0.01)
BK VL ≥50% reduction, n (%)	7 (88)	7 (88)	2 (50)
Change in eGFR⁺, median mL/min/1.73 m^2 (min, max)	-5 (-11, 6)	0 (-16, 9)	-7 (-21, 9)

- 1° endpoint: safety and tolerability through Week 24
- **Posoleucel antiviral activity greatest in patients with high BK viral load**

- Safety profile consistent with that observed in stem cell transplant recipients

Posoleucel (PSL) is an off-the-shelf allogeneic multivirus-specific T cell therapy targeting BKV.

(NCT04605484)

A Randomized Phase 2 Study of MAU868 vs Placebo for BK Viremia in Kidney Transplant Recipients: BK Viral Kinetics and Outcomes in Two Dosing Cohorts

Stanley C. Jordan[1],

HIGHLIGHTS
AMERICAN TRANSPLANT CONGRESS
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POLYOMA VIRUS BK

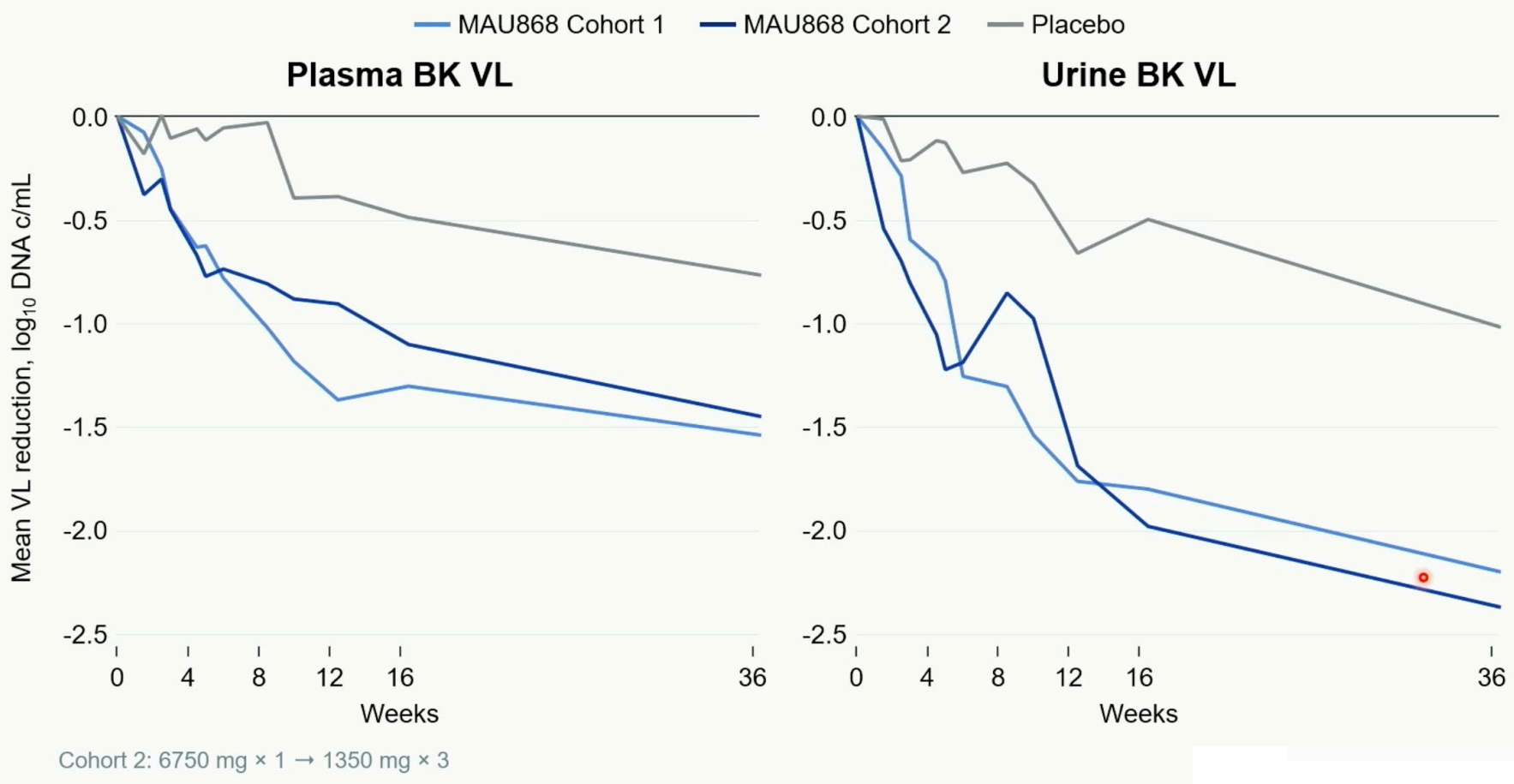
MAU 868

PHASE II. DOBLE CIEGO N=. BIEN TOLERADO. EFICAZ (VIREMIA): + DOSIS = -DOSIS VS PLACEBO

MAU868

Kidney Trans
Patients with BK
2:1
Randomiza

MAU86



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NUEVAS GUÍAS BK (AGOSTO 2022) DRAFT.

HIGHLIGHTS
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IMPACT - Looking to the Future: Overview of New Consensus Guidelines for Defining BK Viral Disease in Renal Transplant
7:00AM-8:00AM Jun 6 (Pacific) Ballroom 6B Upper Leve

Hans H. Hirsch and Camille N. Kotton

DRAFT AGOSTO 2022

Treatment 1 (Selection TTS Consensus WG4)

Treatment 2 (Selection TTS Consensus WG4)

Cost/Benefit and Retransplant (Selection TTS Consensus WG6)

Routine screening for BKPyV-DNA-emia using the proposed strategies as detailed in this current guideline is associated with improvement in clinical outcomes and is cost-effective in kidney transplant recipients. (A, moderate)
We do not recommend deceasing the frequency of screening because it may reduce the efficacy and increase the overall direct healthcare costs. (A, weak)
We recommend re-transplantation in otherwise eligible patients who lost their prior allograft from BKPyVAN. (A, moderate)
We do not recommend routine graft nephrectomy prior to re-transplantation in those patients with allograft failure from BKPyVAN and with undetectable BKPyV-DNAemia. (A, weak)

AÚN NO INCLUÍDOS LOS NUEVOS FÁRMACOS

Diagnostics 1 (Selection TTS Consensus WG3)

Diagnostics 2 (Selection TTS Consensus WG3)

Further data are needed before *pre*-transplant BKPyV serology in the donor and recipient may be considered to risk stratify kidney transplant recipients for the development of BKPyV DNAemia. A barrier to routine clinical use of BKPyV IgG is the lack of standardization of such assays as well as poor commercial availability (one commercially available test).
We do not recommend *pre*-transplant BKPyV-specific T-cell measurement to predict post-transplant BKPyV DNAemia after kidney transplantation. (D, weak)
We do *not* recommend *post*-transplant serologic monitoring for the prediction of BKPyV DNAemia (A, low)
We suggest monitoring *post*-transplant BKPyV-specific T-cell, if available, to predict dynamics of viral replication and to modulate immunosuppression after kidney transplantation. (D, weak)
An allograft biopsy is not necessary during BKPyV DNAemia *unless* rejection is a matter of concern and its detection will alter management. (D, weak)
Screening for BKPyV DNAemia should resume for a few months in case of re-increased maintenance immunosuppression or anti-rejection therapy. (D, low)

Transplantation

Neutropenia/Leukopenia and Viral Resistance With Letermovir (LET) vs Valganciclovir (VGCV) as Cytomegalovirus (CMV) Prophylaxis in Adult Kidney Transplant Recipients (KTRs): Results of a Pivotal Randomized Phase 3 Trial

Flavio Vincenti, MD[1];

NCT03443869

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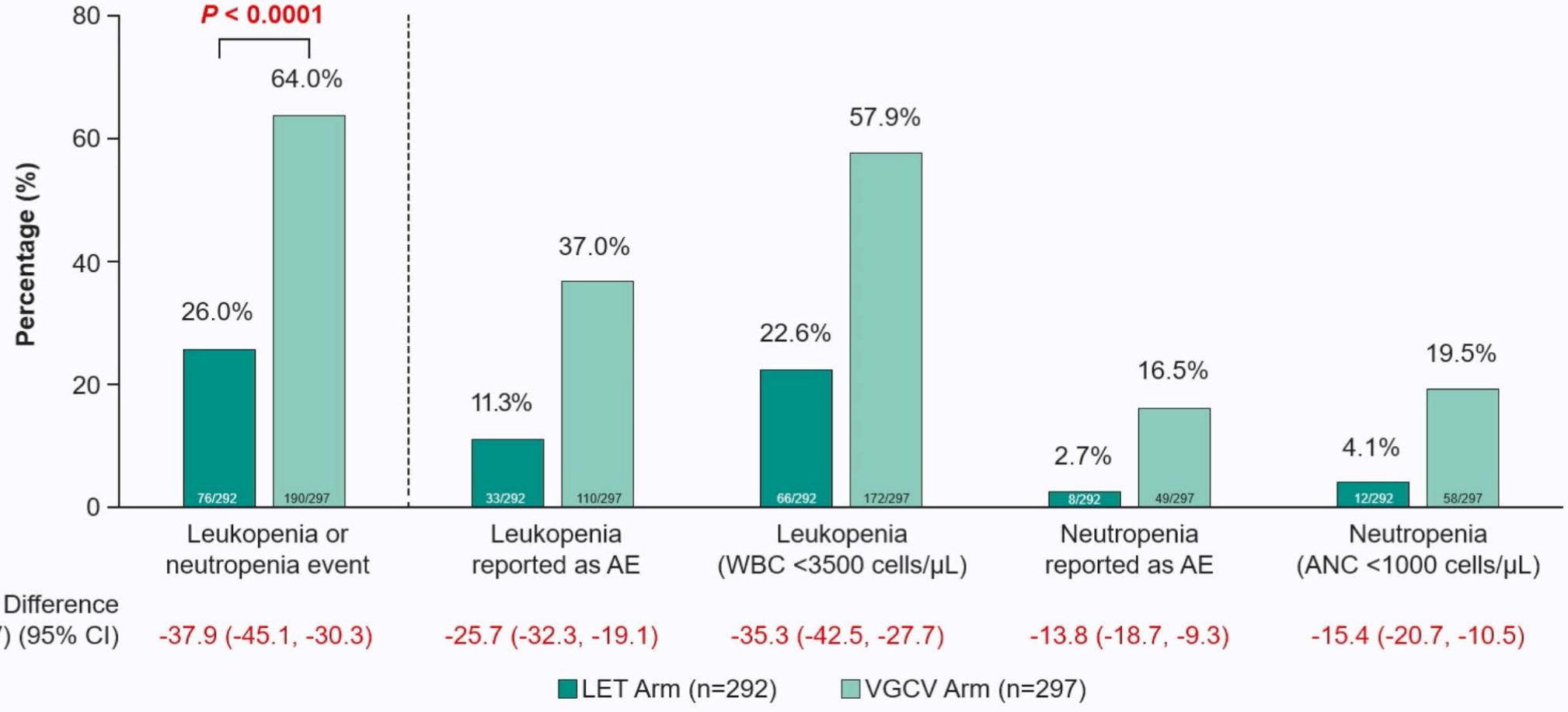
CITOMEGALOVIRUS

Significantly lower rates of leukopenia or neutropenia reported as an AE or laboratory value with LET prophylaxis compared to VGCV prophylaxis



CUIDADOS PALIATIVOS EN TRASPLANTE

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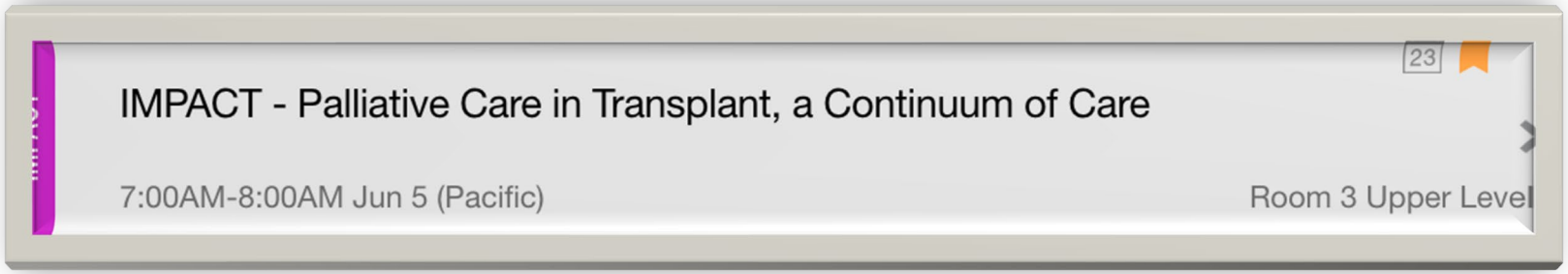

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Why consider palliative?

- Transplant patients have a variable illness course
- Patients can die on the waitlist, have complications, or may not be eligible for transplant
- Better understanding of patient's and caregiver's expectations
- Help with the "hard conversations"
  - Goals of care
  - Advance Care Planning
- Relieve caregiver burden

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Benefits of Palliative Care for Transplant

Care Coordination

- Consultative service
- Services outside of medical needs
- May see patient in their home
- Additional support for caregivers

Shared Decision Making & Trust

- Set appropriate expectations to meet a patient's goals
- Long term relationship throughout the spectrum of care

How to incorporate palliative care into [redacted] transplant evaluation?

Advance Care Planning

- Unique challenges facing potential transplant patients
- Traditional advanced directives do not meet these challenges
- ***Preparedness plans*** allow more nuanced and disease specific discussion about goals and values

Post Transplant Care

- Goals of Care
  - Understanding patient's ongoing and changing goals and preferences
- Psychological and Spiritual Support
  - Important if inadequate quality of life post transplant
  - Caregiver support
- End of life care
  - Transition to hospice if appropriate
  - Symptom management

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MENSAJES PRAA CASA

DESENSIBILIZACIÓN: CARFILZOMIB, TOZILIZUMAB, DARATUMUMAB, ISATUXIMAB

INFECCIONES: BK (POSOLEUCEL, MAU 688, AC NEUTR), CMV(LETERMOVIR, FIZTASOVIMAB), HONGOS (OLOROFIM)

INFECCIONES: EVITAR MULTIRESISTENCIAS, CICLOS ANTB MÁS CORTOS, MEJORES DIAGNÓSTICOS, NUEVOS ANTB

BIOMARCADORES: ESTUDIOS MOLECULARES: ORINA, BIOPSIAS, INTELIGENCIA ARTIFICIAL

CUIDADOS PALIATIVOS: UN ABORDAJE INTEGRAL TAMBIÉN NECESARIO EN TRASPLANTE