

TOLERANCE IN SOLID ORGAN TRANSPLANTATION: UPDATE 2016

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TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **WHAT IS THE
DEFINITION OF
TOLERANCE?**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **DEFINITION OF TOLERANCE**
 - **IMMUNOLOGIC TOLERANCE**: - SPECIFIC IMMUNOLOGIC UNRESPONSIVENESS TO SPECIFIC DONOR TISSUE
 - **OPERATIONAL TOLERANCE** : - LONG-TERM (> 1YR) ALLOGRAFT ACCEPTANCE (CLINICALLY STABLE GRAFT FUNCTION) WITHOUT THE REQUIREMENT FOR CONTINUOUS IMMUNOSUPPRESSION
 - **PROPE TOLERANCE** : “ALMOST TOLERANCE” WHEREBY STABLE ALLOGRAFT FUNCTION IS MAINTAINED BY LOW DOSE NONTOXIC DOSES OF IMMUNOSUPPRESSION WHICH MAY NOT BE REQUIRED INDEFINITELY

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- THE ABILITY TO PRODUCE IMMUNOLOGIC UNRESPONSIVENESS – IMMUNOLOGIC TOLERANCE – WAS FIRST DEMONSTRATED EXPERIMENTALLY BY BILLINGHAM, BRENT & MEDAWAR WHEN THEY SHOWED THAT INNOCULATION OF FETAL MICE OR CHICK EMBRYOS WITH DONOR TISSUE RESULTED IN PERMANENT ACCEPTANCE OF DONOR SKIN ALLOGRAFTS AFTER BIRTH OR HATCHING. THIRD PARTY ALLOGRAFTS WERE REJECTED.

NATURE 172:603, 1953

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

**WHY IS IT IMPORTANT
TO ACHIEVE SOME
FORM OF TOLERANCE?**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **IMPORTANCE OF ACHIEVING TOLERANCE IN SOLID ORGAN ALLOGRAFT RECIPIENTS**
 - **DESPITE DRAMATIC IMPROVEMENT IN SHORT-TERM RENAL ALLOGRAFT FUNCTION WITH CURRENT IMMUNOSUPPRESSIVE AGENTS LONG-TERM ALLOGRAFT SURVIVAL RATES HAVE IMPROVED MINIMALLY ESPECIALLY RENAL ALLOGRAFTS**
 - **SIDE EFFECTS FROM IMMUNOSUPPRESSIVE AGENTS PRODUCE SIGNIFICANT MORBIDITY AND ADVERSELY IMPACT ON THE QUALITY OF LIFE AS WELL AS LONG TERM GRAFT AND PATIENT SURVIVAL RATES**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

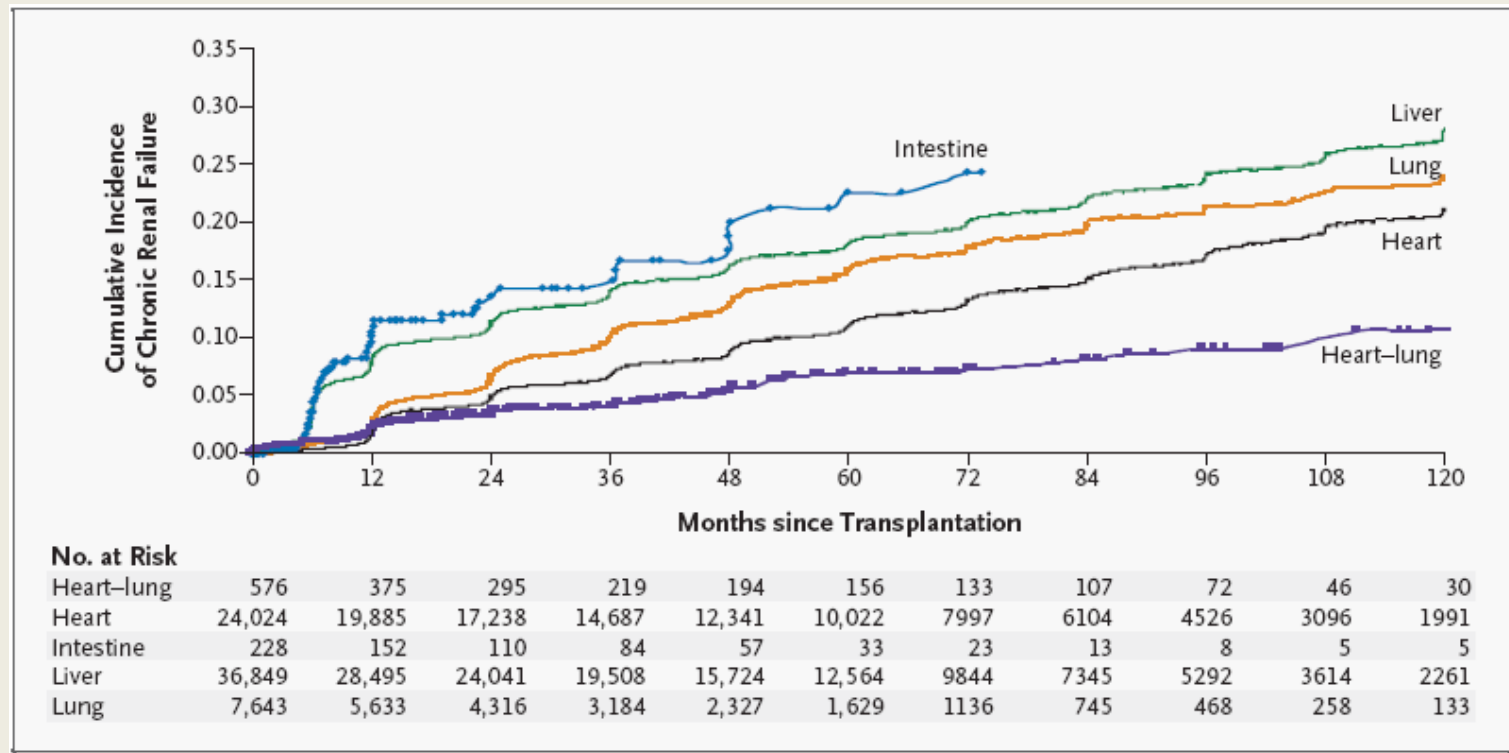
Cohort Group	GRAFT SURVIVAL RATES					
	LIVING DONOR			DECEASED DONOR		
	1yr	3yr	5yr	1yr	3yr	5yr
1987-1991	90.3	82.4	76.3	76.4	65.3	56.9
1992-1996	92.1	87.0	81.6	87.0	77.9	70.9
1997-2001	95.4	91.4	86.3	93.1	84.5	78.3
2002-2006	96.3	92.0	86.4	94.4	84.1	79.2
2007-2013	96.4	93.4	--	95.8	90.4	--

DD APPROXIMATING LD SURVIVAL AT 1, 3 YEARS FOR THE MOST RECENT COHORT

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **SIDE EFFECTS FROM IMMUNOSUPPRESSIVE AGENTS**
 - **MALIGNANCY**
 - **CARDIOVASCULAR DISEASE**
 - **NEPHROTOXICITY**
 - **GROWTH RETARDATION**
 - **COSMETIC SIDE EFFECTS**
 - **NON-ADHERENCE**

CUMULATIVE INCIDENCE OF CHRONIC RENAL FAILURE AMONG 69,321 PERSONS WHO RECEIVED NONRENAL ORGAN TRANSPLANTS IN THE UNITED STATES 1990-2000



OJO ET AL NEJM SEPT 4, 2003 349:931-940

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- THEREFORE, ACHIEVING PROPE OR CLINICAL OPERATIONAL TOLERANCE (**COT**) WOULD POTENTIALLY EXTEND ALLOGRAFT LONGEVITY (**ALLEVIATE NEPHROTOXICITY**) AND MAXIMIZE THE QUALITY OF LIFE OF RECIPIENTS
- IN ADOLESCENTS AND YOUNG ADULTS IT WOULD ALLEVIATE THE IMPACT ON **NON-ADHERENCE** (NA) ON LONG-TERM ALLOGRAFT FUNCTION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHAT IS THE CURRENT STATUS OF
CLINICAL OPERATION TOLERANCE
(*COT*)?

WHAT *GROUPS* OF SOLID ORGAN
TRANSPLANT RECIPIENTS HAVE
EXHIBITED *COT*?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL OPERATIONAL TOLERANCE (**COT**)
 - THOSE WHO EXHIBITED **NON-ADHERENCE** (NA) TO IMMUNOSUPPRESSIVE MEDICATIONS
 - THOSE WHO UNDERWENT **PLANNED WEANING** OR DISCONTINUATION OF IMMUNOSUPPRESSIVE MEDICATIONS BECAUSE OF SEVERE TOXICITY OR LIFE-TREATENING COMPLICATIONS (PTLD, INFECTION)
 - **PROTOCOLS** FOR PLANNED WEANING AND EVENTUAL DISCONTINUATION OF ALL IMMUNOSUPPRESSIVE MEDICATIONS IN CLINICALLY STABLE LONG-TERM SURVIVORS (LIVER TRANSPLANT RECIPIENTS)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL OPERATIONAL TOLERANCE (*COT*)
 - PROTOCOLS COMBINING HEMATOPOETIC CELL AND KIDNEY TRANSPLANTATION FROM THE SAME DONOR WITH NONMYELOABLATIVE CONDITIONING TO ESTABLISH TEMPORARY OR PERSISTENT MIXED CHIMERISM WITH SUBSEQUENT RAPID DISCONTINUATION OF IMMUNOSUPPRESSIVE THERAPY

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT WERE THE DATA
DOCUMENTING CLINICAL
OPERATIONAL TOLERANCE
(*COT*) IN RENAL ALLOGRAFT
RECIPIENTS?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- ***COT* : NON-ADHERENCE (RENAL)**
 - '75 - '76 : INITIAL REPORTS OF 23 *NA* RECIPIENTS
 - ❖ 17 REJECTED
 - ❖ 6 HAD “STABLE” GRAFT FUNCTION FOR 17-60 MO.
 - '75 & '80 : NATIONAL SURVEYS IN UNITED STATES
 - ❖ 24 RECIPIENTS OFF IMMUNOSUPPRESSION WITH ONLY 2 SUSTAINED FOR 9 AND 36 MO.
 - ❖ 23 RECIPIENTS OFF IMMUNOSUPPRESSION FOR > 8 MO. WITH 6 > 3 YEARS
 - '96 : ONE RECIPIENT WAS *NA* DURING PREGNANCY AND REMAINED OFF IMMUNOSUPPRESSION FOR 9 YEARS WITH NORMAL ALLOGRAFT FUNCTION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **CLINICAL OPERATIONAL TOLERANCE (*COT*)**
 - '06 : 10 RECIPIENTS OFF IMMUNOSUPPRESSION FOR 1 TO 20 YEARS (FRANCE)
 - ❖ 7 NON-ADHERENT AND 3 PTLD/MALIGNANCY
 - ❖ 5 HAD A PRIOR ACUTE REJECTION EPISODE
 - ❖ 2 HAD DECLINE IN ALLOGRAFT FUNCTION AFTER 9 AND 13 YEARS OFF IMMUNOSUPPRESSION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **CLINICAL OPERATIONAL TOLERANCE (*COT*)**
 - '10 : 11 RECIPIENTS (EUROPEAN CONSORTIUM FOR TOLERANCE – 3 FROM FRANCE)
 - ❖ 8 NA , 1 MALIGNANCY, 1 BMT (SAME DONOR), 1 ?
 - ❖ 3 < 21 YEARS OLD
 - ❖ OFF IMMUNOSUPPRESSION 3 – 21 YEARS
 - '10 : 25 RECIPIENTS (AMERICAN NETWORK FOR IMMUNE TOLERANCE)
 - ❖ 20 NA, 2 MEDICAL, 3 ?
 - ❖ OFF IMMUNOSUPPRESSION 1 -32 YEARS

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT WERE THE DATA DOCUMENTING CLINICAL OPERATIONAL TOLERANCE (*COT*) IN LIVER TRANSPLANT RECIPIENTS?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **COT: NON-ADHERENCE (LIVER)**
 - 5 RECIPIENTS 12 1/2 -18 2/3 YEARS POST – TRANSPLANT WHO WERE OFF IS FOR 5 -11 YEARS.
 - ALL HAD DONOR MICROCHIMERISM (**STARZL: HEPATOLOGY 17:1127, 1993**)
 - FOLLOW-UP 4 ½ YEARS LATER (**MAZARIEGOS ET AL: TRANSPLANTATION 63:243,1997**)
 - ❖ ONE DIED IN A VEHICULAR ACCIDENT
 - ❖ ONE WAS RETRANSPLANTED WITH CHRONIC HEPATITIS C INFECTION 9 YEARS OFF IMMUNOSUPPRESSION
 - ❖ 3/5 HAVE NORMAL ALLOGRAFT FUNCTION 14 -17 YEARS OFF IMMUNOSUPPRESSION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

IS THERE A ***SIGNATURE BIOMARKER***
THAT CAN IDENTIFY THE RECIPIENT
WITH CLINICAL OPERATION
TOLERANCE (***COT***)?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- NEWELL (JCI 120:1836,'10)
 - 25 RECIPIENTS WITH *COT* OFF *IS* 1 -32 YEARS (US NETWORK OF IMMUNE TOLERANCE)
 - COMPARED GENE EXPRESSION PROFILES AND PERIPHERAL BLOOD LYMPHOCYTE SUBSETS OF TOLERANT RECIPIENTS WITH THOSE RECEIVING *IS* DRUGS AND HEALTHY CONTROLS
 - TOLERANT GROUP HAD *B CELL SIGNATURE* WITH UPREGULATION OF CD20 mRNA IN URINE CELLS
 - *3 B CELL DIFFERENTIATION GENES* DISTINGUISHED TOLERANT FROM NON-TOLERANT RECIPIENTS

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

DO LIVER TRANSPLANT
RECIPIENTS WITH CLINICAL
OPERATIONAL TOLERANCE
(*COT*) HAVE A DISTINCT
BIOMARKER PROFILE?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- PROFILING OF *COT* LIVER RECIPIENTS
 - 17 *COT* ; 21 *NON-COT*; 16 HEALTHY CONTROLS
 - MICROARRAYS/REAL-TIME *PCR* IDENTIFIED GENE SIGNATURES (T CELLS) DISCRIMINATING *COT* AND *NON-COT* RECIPIENTS WITH ACCURACY
 - PERIPHERAL BLOOD LYMPHOCYTE PROFILING IDENTIFIED TOLERANCE ASSOCIATED TRANSCRIPTIONAL PATTERNS

MARTINEZ-LLOREDELLA ET AL JCI 118:2545, 2008

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- DO THE MICROARRAY AND REAL-TIME PCR GENE EXPRESSION AND PERIPHERAL BLOOD IMMUNOTYPING OR BIOMARKER IDENTIFICATION PROVIDE A “FINGERPRINT” THAT IS SIMILAR IN LIVER AND KIDNEY OPERATIONALLY TOLERANT RECIPIENTS?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- LOZANO ET AL [AJT 11:1916, 2011](#)

- RECIPIENTS STUDIED

- ❖ KIDNEY (N=12) - STABLE OFF IMMUNOSUPPRESSION
2 -13 YEARS
- ❖ KIDNEY (N=12) - STABLE IMMUNOSUPPRESSION
> 3 YEARS
- ❖ KIDNEY (N=12) - **CAN** WITH C4d DEPOSITS AND DSA
- ❖ LIVER (N=12) - STABLE OFF IMMUNOSUPPRESSION
1 - 2 ½ YEARS PER WEANING PROTOCOL
- ❖ LIVER (N=12) - STABLE ON IMMUNOSUPPRESSION
> 3 YEARS FOLLOWING FAILURE OF WEANING PROTOCOLS
- ❖ HEALTHY VOLUNTEERS (N=12)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- LOZANO ET AL [AJT 11:1916, 2011](#)
 - LIVER AND KIDNEY TOLERANT RECIPIENTS DIFFERED FROM BOTH NON-TOLERANT RECIPIENTS AND HEALTHY VOLUNTEERS IN TRANSCRIPTIONAL GENE EXPRESSION PROFILES
 - MINIMAL OVERLAP IN LIVER AND KIDNEY TOLERANT RELATED GENE EXPRESSION DATASETS
 - TOLERANT KIDNEY RECIPIENTS EXHIBITED PERIPHERAL **BLOOD B - CELL** PHENOTYPIC MARKERS WHICH WERE NOT PRESENT IN TOLERANT LIVER RECIPIENTS

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT IS THE CURRENT STATUS OF BIOMARKERS (IDENTIFY GENES BY MICROARRAY TRANSCRIPTIONAL PROFILING AND VALIDATED BY A qPCR TRANSCRIPTIONAL PLATFORM UTILIZING PERIPHERAL BLOOD MONONUCLEAR CELLS) TO ACCURATELY SEPARATE POTENTIALLY CLINICALLY OPERATIONALLY TOLERANT RECIPIENTS FROM NON-TOLERANT RECIPIENTS OF LIVER/KIDNEY ALLOGRAFTS? (**LONDOÑO ET AL AJT 12:1370,2012**)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- NATURAL KILLER (NK) CELL TRANSCRIPTS MOST ROBUST MARKERS IN LIVER TRANSPLANT RECIPIENTS WITH COT
- “B” CELL GENE EXPRESSION MOST ROBUST IN KIDNEY TRANSPLANT RECIPIENTS WITH COT
- TISSUE GENES INVOLVED IN IRON HOMEOSTASIS IN LIVER TRANSPLANT RECIPIENTS PRIOR TO TRANSPLANTATION (BOHNE ET AL JCI 122:368, 2012)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- THEREFORE, AT PRESENT THERE IS NO ROBUST *BIOMARKER FINGERPRINT* THAT CAN IDENTIFY THE POTENTIAL RECIPIENT WHO MAY MANIFEST CLINICAL OPERATIONAL TOLERANCE?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHAT ARE THE DATA FROM
PROSPECTIVE WEANING
PROTOCOLS IN PEDIATRIC LIVER
ALLOGRAFT RECIPIENTS?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **KYOTO EXPERIENCE ('90 – '08) (LIVING RELATED DONORS)**
 - **200 - WEANING ATTEMPTED**
 - ❖ **154 - ELECTIVE**
 - ❖ **48 - NON-ELECTIVE (NA, PTLD, INFECTION**
 - **84 - SUCCESSFUL (15% OF TOTAL TRANSPLANTED)**
 - **50 - UNSUCCESSFUL**
 - ❖ **24 - REJECTED**
 - ❖ **26 - FIBROSIS ON BIOPSY**
 - **66 - UNDERGOING WEANING PROCESS**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **KYOTO EXPERIENCE ('90 – '08) (LRD's)**
 - **50% OF TOLERANT RECIPIENTS EXHIBITED ALLOGRAFT FIBROSIS DESPITE NORMAL LIVER FUNCTION TESTS**
 - **REINTRODUCTION OF IMMUNOSUPPRESSION LEAD TO REDUCTION IN FIBROSIS IN 50% OF THE TOLERANT RECIPIENTS**

OHE ET EL TRANSPLANTATION 90:325, 2010

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **IMMUNE TOLERANCE
NETWORK/NATIONAL INSTITUTE OF
ALLERGY AND INFECTIOUS DISEASE
(USA) FUNDED TRIAL IN 2 CENTERS**
- **20 STABLE PEDIATRIC LIVING RELATED
DONOR LIVER TRANSPLANT RECIPIENTS
HAD IMMUNOSUPPRESSION
WITHDRAWN OVER 36 WEEKS**

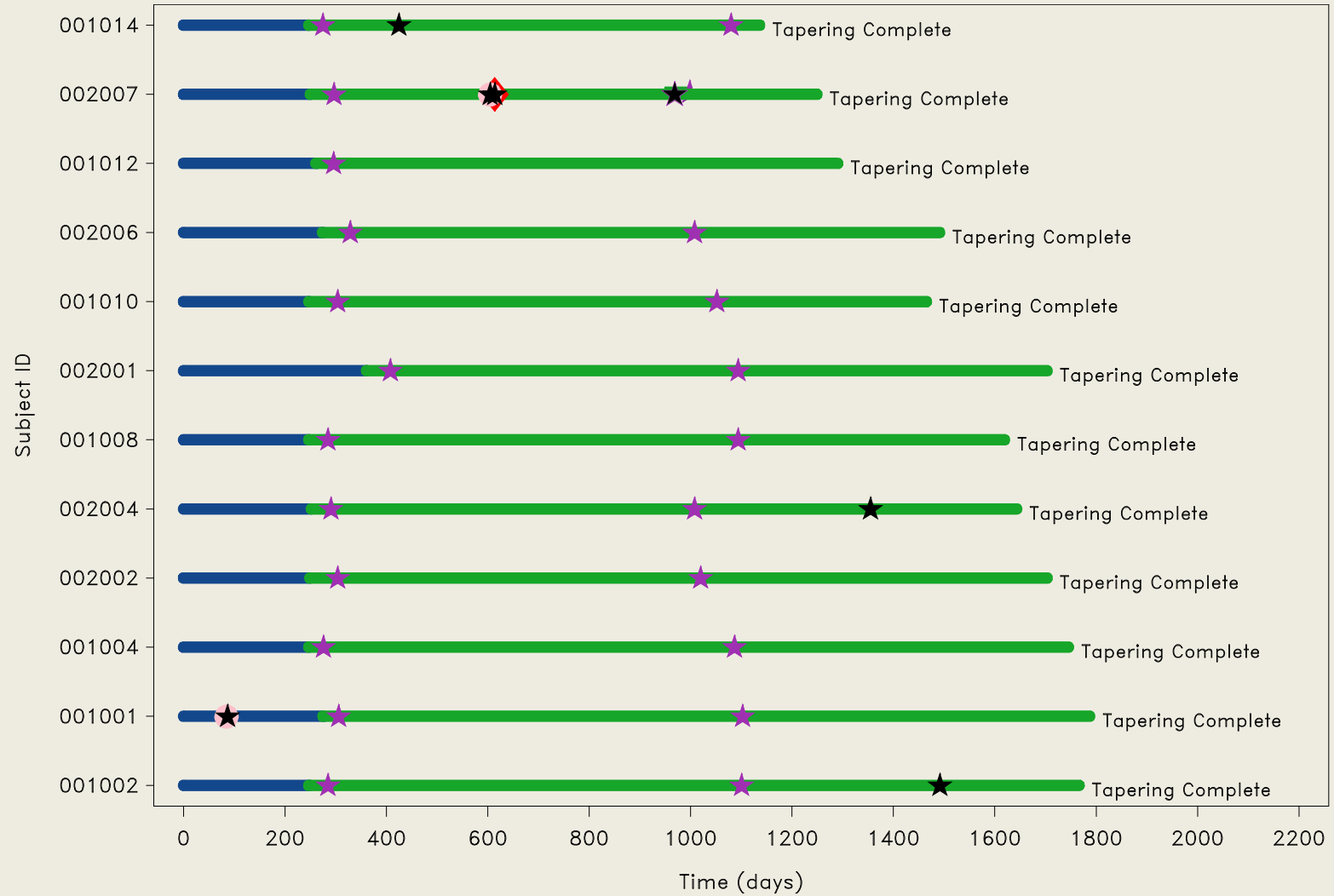
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **PARENTAL LIVING DONOR TRANSPLANT**
- **<18 YEARS OLD AT TIME OF TRANSPLANT**
- **≥4 YEARS SINCE TRANSPLANT**
- **SCREENING LIVER BIOPSY**
 - **NO ACUTE OR CHRONIC REJECTION**
 - **FIBROSIS < STAGE 2 (ISHAK)**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION: CONTRAINDICATIONS

- **AUTOIMMUNE LIVER DISEASE: AIH / PBC / PSC**
- **HEPATITIS B OR C**
- **SECOND ORGAN TRANSPLANT**
- **AST OR ALT >2X ULN**
- **TOTAL + DIRECT BILIRUBIN & ALK PHOS OR GGT >2X ULN**
- **EVIDENCE OF AUTOIMMUNITY (IGG; SEROLOGY)**
- **CHANGE IN LIVER TESTS IN PRECEDING 2 MONTHS**
- **GFR <40 ML / MIN / 1.73 M²**
- **RECENT INCREASE IN IMMUNOSUPPRESSION**

12 OF 20 PARTICIPANTS MET THE PRIMARY ENDPOINT: OFF IMMUNOSUPPRESSION FOR 29.2 – 49.9 MONTHS



- Tapering
- IS Free
- ★ Per-Protocol Biopsy
- Allograft Dysfunction
- ★ For-Cause Biopsy
- ◆ Biopsy-Proven Rejection-Central



TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- ADDITIONAL PROTOCOL EXPANDED TO 12 CENTERS AND INCLUDED DECEASED DONOR (65%) PEDIATRIC LIVER Tx RECIPIENTS
- 55/88 (62.5%) COMPLETED WITHDRAWAL IMMUNOSUPPRESSION AND 43/88 (49%) HAVE REMAINED OF IMMUNOSUPPRESSION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **WHAT IS THE CURRENT STATUS OF *PLANNED WEANING* OF IMMUNOSUPPRESSION IN ADULT LIVER TRANSPLANT RECIPIENTS?**

SANCHEZ-FUEYO LIVER TRANSPLANT 17:S69, 2011

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- SUCCESSFUL WEANING OCCURS IN ABOUT **20%** OF LIVER TRANSPLANT RECIPIENTS
- THE TRUE INCIDENCE OF POTENTIAL SPONTANEOUS COT IS UNKNOWN
- PREVALENCE OF COT IS INCREASED IN PEDIATRIC RECIPIENTS UNDERGOING TRANSPLANTATION @ <1 YEAR OF AGE AND IN ADULT RECIPIENTS >10 YEARS POST-TRANSPLANT

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL REJECTION DURING WEANING IS MILD AND VERY RESPONSIVE TO TREATMENT WITH INCREASED IMMUNOSUPPRESSION
- COT RECIPIENTS EXHIBIT TRANSCRIPTIONAL PATTERNS IN BOTH BLOOD AND LIVER TISSUE
- THE LONG-TERM REDUCTION IN MORBIDITY AND MORTALITY FOLLOWING WITHDRAWAL OF IMMUNOSUPPRESSION REMAINS UNKOWN

SANCHEZ-FUEYO LIVER TRANSPLANT 17:S69, 2011

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- ARE THERE ANY CLINICAL PHENOTYPES PREDICTIVE OF COT?
 - 33/75 LIVER TRANSPLANT RECIPIENTS >3 YEARS POST-TRANSPLANT HAD STALBE LIVER FUNCTION FOR ONE YEAR FOLLOWING PLANNED WITHDRAWAL OF IMMUNOSUPPRESSIVE TREATMENT

BOHNE ET AL JCI 122:368,2012

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

— COT RECIPIENTS COMPARED TO NON-COT
RECIPIENTS:

- ❖ HAD BEEN TRANSPLANTED FOR A *LONGER*
PERIOD OF TIME ($p < 0.0001$)
- ❖ WERE *OLDER* ($p < 0.0005$)
- ❖ WERE *NOT* RECEIVING A CALCINEURIN
INHIBITOR ($p < 0.014$)

BOHNE ET AL JCI 122:368, 2012

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **WHAT ARE REGULATORY “T” CELLS (Treg)?**
 - A DISTINCT “T” CELL POPULATION, PRODUCED IN THE THYMUS, (PREVIOUSLY KNOWN AS SUPPRESSOR “T” CELLS) THAT MODULATE THE IMMUNE SYSTEM, RETAIN SELF-TOLERANCE AND ELIMINATE AUTOIMMUNITY
 - Treg MAINTAIN SELF-TOLERANCE AND HOMEOSTASIS BY SUPPRESSING ABERRANT OR EXCESSIVE IMMUNE RESPONSES

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT ARE THE MECHANISMS
OF Treg CELL
IMMUNOSUPPRESSION?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- SUPPRESS ACTIVITY OF ANTIGEN PRESENTING CELLS (*APCs*) AND EFFECTOR “T” CELLS (*Teff*) BY DIRECT CONTACT
- SUPPRESS *APCs* (DENTRITIC CELLS) FUNCTION AND MATURATION BY SUPPRESSIVE CYTOKINES *IL10* AND *TGFβ*
- DESTROY *Teff* THROUGH SECRETORY PERFORIN AND GRANZYME A

HAQUE ET AL FRONTIERS IN ONCOLOGY 4:1,2014

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT IS THE USUAL NUMBER OF Treg CELLS IN HUMANS?
 - 70 kg YOUNG ADULT HUMAN
 - ❖ 460×10^9 LYMPHOCYTES
 - ❖ 165×10^9 CD4+ “T”CELLS
 - ❖ 13×10^9 Treg CELLS

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT CLINICAL STUDIES IN HUMANS HAVE LED TO THE DEVELOPMENT OF PROTOCOLS FOR THE USE OF EX-VIVO EXPANDED Treg CELLS FOR INFUSION FOLLOWING SOLID ORGAN TRANSPLANTATION?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- EX-VIVO EXPANSION OF DONOR Treg TO TREAT CHRONIC GVHD (TRZONKOWSKI ET AL CLINICAL IMMUNOLOGY 133:22, 2009)
- EX-VIVO EXPANSION OF THIRD PARTY UMBILICAL CORD BLOOD (UCB) Treg TO PREVENT GVHD IN RECIPIENTS OF UCB STEM CELL TRANSPLANTS (BRUNSTEIN ET AL BLOOD 117:1061, 2011)
- EX-VIVO EXPANSION OF DONOR Treg FROM HLA-HAPLOIDENTICAL HSCT RECIPIENTS TO PREVENT GVHD (IANNI ET AL BLOOD 117:3921, 2011)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- EX-VIVO EXPANSION OF AUTOLOGOUS Treg IN 10 CHILDREN (8-16 y/o) WITHIN 2 MONTHS OF ONSET OF TYPE 1 DIABETES MELLITUS
 - ❖ @ 11 MONTHS POST-INFUSION 2 PATIENTS WERE OFF INSULIN AND 8 PATIENTS WERE RECEIVING <0.5 IU/kg OF INSULIN (MAREK-TRZONKOWSKA ET AL PEDIATR DIABETES 14:322, 2013)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT IS THE CURRENT STATUS OF THE USE OF Treg IN CLINICAL SOLID ORGAN TRANSPLANTATION?
 - PROTOCOLS ARE IN PLACE TO USE EX-VIVO EXPANDED AUTOLOGOUS Treg AS WELL AS DONOR ALLOANTIGEN-REACTIVE Treg (darTreg) IN LIVER AND KIDNEY TRANSPLANTATION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- WHAT ARE THE DATA DEMONSTRATING THE ABILITY TO ACHIEVE CLINICAL OPERATIONAL TOLERANCE IN LIVER TRANSPLANT RECIPIENTS WITH EXPANDED AUTOLOGOUS *darTregs* BASED TREATMENT?

TODO ET AL HEPATOLOGY 2016

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- 10 ADULT LIVING DONOR LIVER TRANSPLANTS
- AUTOLOGOUS EXPANDED darTregs FOLLOWING CO-CULTURE WITH IRRADIATED DONOR CELLS
- CYCLOPHOSPHAMIDE (40mg/kg) ON POD 5
- darTregs INFUSED ON POD 13
- ↓ IMMUNOSUPPRESSION (STERIODS AND *MMF* ↓ @ 1 MO) (↓ TACROLIMUS STARTED @ 6 MONTHS AND COMPLETED @ 18 MO)

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- 7/10 COMPLETED WEANING FROM TACROLIMUS AND ARE OFF TACROLIMUS FOR 16 – 33 MONTHS WITH 4 FOR > 24 MONTHS
- 3/10 WITH *AUTOIMMUNE* LIVER DISEASES DEVELOPED MILD REJECTION AND RESUMED IMMUNOSUPPRESSIVE THERAPY

TODO ET AL HEPATOLOGY 2016

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHAT IS THE CURRENT STATUS OF
INDUCING TEMPORARY OR PERSISTENT
CHIMERISM WITH *SAME DONOR*
KIDNEY AND HEMATOPOETIC CELL
TRANSPLANTATION TO FACILITATE
RAPID DISCONTINUATION OF ALL
IMMUNOSUPPRESSION?

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **KIDNEY AND HEMATOPOETIC CELL Tx**
 - 6 PATIENTS WITH MULTIPLE MYELOMA (MM) AND RENAL FAILURE RECEIVED SIMULTANEOUS KIDNEY AND BONE MARROW Tx FROM *HLA* IDENTICAL DONORS FOLLOWING NONMYELOABLATIVE CONDITIONING
 - 3 RECIPIENTS LOST **CHIMERISM** BUT KIDNEY FUNCTION WAS ACCEPTABLE (SERUM CREATININE 0.9 – 2.0 mg/dl) OFF IMMUNOSUPPRESSION FOR 1.3 TO > 7 YEARS
 - 3 RESUMED IMMUNOSUPPRESSION FOR *GVHD*

FUDABA ET AL AJT 6:2121, 2006

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- KIDNEY AND HEMATOPOETIC CELL Tx
 - 5 PATIENTS RECEIVED COMBINED BONE MARROW AND KIDNEY Tx FROM **ONE-HAPLOTYPE MISMATCHED LIVE-RELATED DONORS** WITH NON-MYELOABLATIVE CONDITIONING
 - TRANSIENT **CHIMERISM** AND REVERSIBLE **CAPILLARY LEAK SYNDROME** OCCURRED IN ALL RECIPIENTS
 - IRREVERSIBLE ACUTE HUMORAL REJECTION OCCURRED IN ONE RECIPIENT
 - IMMUNOSUPPRESSION WAS DISCONTINUED IN 4/5 RECIPIENTS @ 9 -14 MO. AND RENAL FUNCTION WAS STABLE FOR 2 – 5.3 YEARS

KAWAI ET AL NEJM 358:353, 2008

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **ENGRAFTMENT SYNDROME**
 - 10 RECIPIENTS WITH KIDNEY AND BONE MARROW FROM ONE-HAPLOTYPE MISMATCHED PARENT/SIBLING DONOR
 - 9/10 DEVELOPED SEVERE CAPILLARY LEAK SYNDROME (ENGRAFTMENT SYNDROME) @ 10 -16 DAYS POST-Tx CAUSING SIGNIFICANT RENAL DYSFUNCTION
 - **2 ALLOGRAFTS WERE LOST**
 - CHIMERISM WAS TRANSIENT AND UNDETECTABLE AFTER DAY 14
 - 8 RECIPIENTS ARE SURVIVING OFF IS 2 MO – 7 YR WITH A SERUM CREATININE OF 1.1 – 2.0 mg/dl
 - ETIOLOGY OF DAMAGE TO ENDOTHELIUM IS OBSCURE

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **WHAT ARE THE LONG-TERM RESULTS OF THE MGH PROTOCOL OF TRANSPLANTATION OF HLA-MISMATCHED LIVE-RELATED DONOR KIDNEY AND BONE MARROW TRANSPLANTATION WITH SUBSEQUENT DISCONTINUATION OF MAINTENANCE IMMUNOSUPPRESSION (IS)?**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **7/10 OFF IMMUNOSUPPRESSION >4 YEARS**
 - **4/7 OFF IMMUNOSUPPRESSION 4.5-11.4 YEARS**
 - **3/7 REINSTITUTION OF IMMUNOSUPPRESSION @ 5-8 YEARS (RECURRENCE OF PRIMARY KIDNEY DISEASE/CHRONIC ANTIBODY MEDIATED REJECTION)**
- **3/10 FAILED FROM TMA/REJECTION**
- **TRANSIENT CHIMERISM ONLY IN ALL RECIPIENTS**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- 12/19 (63%) ENROLLED IN RELATED AND UNRELATED LIVING DONOR KIDNEY Tx PLUS FCRx (POD+1) Tx WITH NONMYELOABLATIVE PRE-Tx CONDITIONING ARE CURRENTLY OFF ALL IMMUNOSUPPRESSION FOR 8 TO 48 MO.
- SERUM CREATININE LEVEL 0.79 – 1.54mg/dl
- 2/19 (10.5%) GRAFTS LOST: *CNI TMA*, INFECTION IN NATIVE *PKD*
- 11/12 OFF ALL Rx PERSISTENTLY 100% CHIMERIC

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

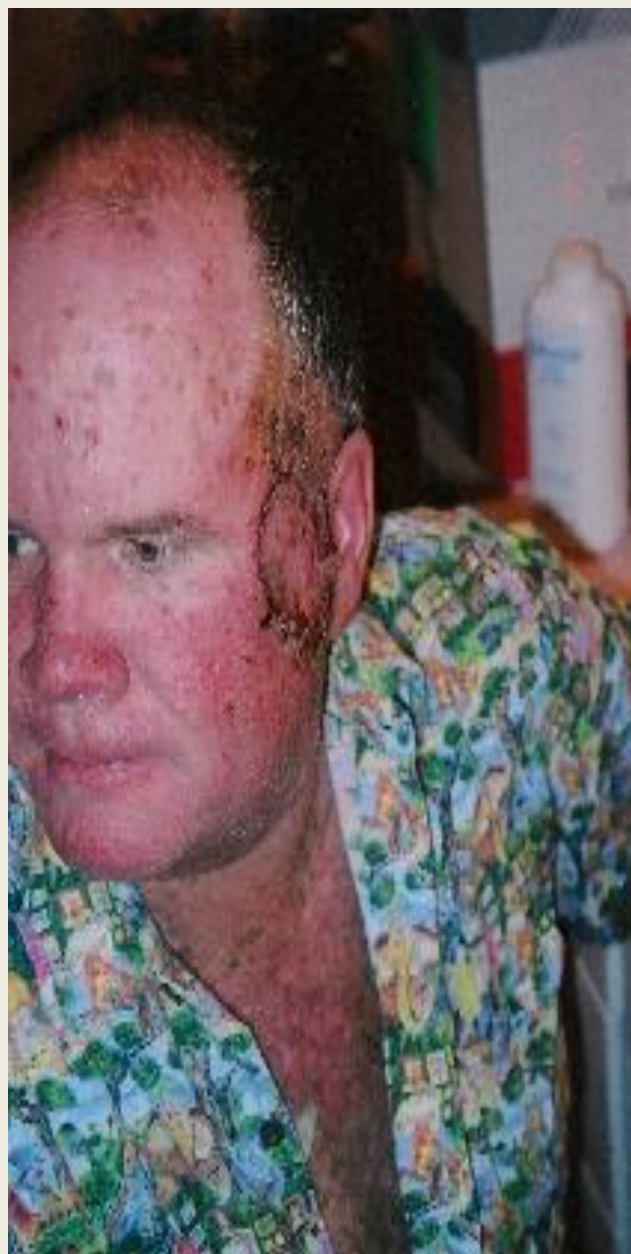
- **WHAT IS A FACILITATING CELL?**
 - 2 PHENOTYPIC POPULATIONS – CD56(bright) AND CD56(neg)- THAT PROMOTE HSC ENGRAFTMENT AND HOMING TO **FACILITATE CHIMERISM**
 - ESTABLISHMENT OF HIGH LEVELS OF **DONOR CHIMERISM** WITHOUT **GVHD** OR **ENGRAFTMENT SYNDROME** FOLLOWING NONMYELOABLATIVE CONDITIONING IN MISMATCHED RELATED AND UNRELATED RECIPIENTS

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **55 YEAR OLD MALE WHO IS 49 YEARS POST LIVE RELATED KIDNEY TRANSPLANT FROM HIS FATHER. INITIAL IMMUNOSUPPRESSION CONSISTED OF AZATHIOPRINE (IMURAN) 50 mg/DAY AND PREDNISONONE 5 mg/DAY. NO CLINICAL REJECTION EPISODES. CURRENT SERUM CREATININE IS 1.7 mg/dl. HE HAS HAD MULTIPLE SKIN CANCERS – BASAL CELL CA, SQUAMOUS CELL CA AND MELANOMA. CURRENTLY ON 100 mg/DAY OF AZATHIOPRINE AND 5mg/DAY OF PREDNISONONE.**









Kidney Transplant – 1967

Splenectomy – 1978

Partial left Orchiectomy due to trauma – 1990's

Basil/Squamous cell carcinoma (left neck) 2003

Melanoma (upper left arm) – 2006

Squamous cell in-situ (right chest) – 2006

Escherichia Coli bacteremia – 2006

Squamous cell/pre/part Aurical Partoid 7-2010

Radiation therapy due to Squamous cell carcinoma Aurical Partoid Oct/Dec-2010

Radiation therapy due to Squamous cell carcinoma Left thumb Dec 2012

Radiation therapy on Right hand above wrist Dec 2012

Osteomyelitis L3-L4 – July/August 2014

Radiation therapy due to Squamous cell on Right Finger March-April 2015

Keratosis' and squamous cell skin issues continuing

PREDNISONE 5MG TABLETS 1 per day

RAPAMUNE 1MG TABLETS .5 per day

OMEGA-3 Salmon Oil 1 gm capsule (a.m. and p.m.)

ATORVASTATIN 20 MG TABLET generic for LIPITOR 1 per day (taken at bedtime)

LEVOTHYROXINE 50 MCG tablet 1 tablet per day

ENALAPRIL MALEATE GENERIC FOR VASOTEC 20 MG TABLET 1 Tablet daily

SODIUM BICARB 650 mg one tablet twice a day

CEPHALEXIN GENERIC FOR KEFLEX 500 MG CAPSULE as needed

VITAMIN D 1000 UNIT TAB

Sometimes VITAMIN C

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

**IS THIS RECIPIENT CLINICALLY OPERATIONALLY
TOLERANT?**

**WOULD IT HAVE BEEN SAFE TO REDUCE AND/OR
ELIMINATE THE AZATHIOPRINE WHICH IN
ADDITION TO ULTRA -VIOLET LIGHT IS
PRODUCING THE SKIN CANCER?**

**IF THERE WAS A TEST TO PROFILE THE RECIPIENT
WITH *COT* IT WOULD BE EASIER TO MAKE A
DECISION REGARDING DISCONTINUATION OF
CURRENT IMMUNOSUPPRESSION!**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **CONCLUSIONS**

- CLINICAL OPERATIONAL TOLERANCE (**COT**) IS BECOMING A THERAPUETIC REALITY WITH THE IMPLEMENTATION OF PROTOCOLS WHICH FACILITATE WEANING OF IMMUNOSUPPRESSIVE MEDICATIONS @ SOME TIME INTERVAL FOLLOWING TRANSPLANTATION

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **CONCLUSIONS**

- **SUCCESSFUL WEANING IN PEDIATRIC (60%) AND ADULT (20%) LIVER TRANSPLANT RECIPIENTS OCCURS PRIMARILY IN LONG-TERM (> 3-5 YRS) SURVIVORS WITH EXCELLENT GRAFT FUNCTION**
- **COMBINED HEMATOPOETIC STEM CELL AND KIDNEY TRANSPLANTATION FROM THE SAME DONOR WITH DEVELOPMENT OF *CHIMERISM* HAS BEEN SUCCESSFUL IN FACILITATING WEANING IN KIDNEY ALLOGRAFT RECIPIENTS**

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **CONCLUSIONS**

- THE EMERGENCE OF THE USE OF EXPANDED AUTOLOGOUS *Treg* CELLS TO FACILITATE WEANING OF IMMUNOSUPPRESSION IN THE IN THE EARLY POST-TRANSPLANT PERIOD APPEARS SUCCESSFUL WITH LIMITED SHORT-TERM SIDE EFFECTS ALTHOUGH THERE ARE LIMITED DATA IN LIVER GRAFT RECIPIENTS

TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **CONCLUSIONS**

- PROFILING OF RECIPIENTS WITH CLINICAL OPERATIONAL TOLERANCE (**COT**) COULD LEAD TO PROSPECTIVE IDENTIFICATION OF RECIPIENTS WHO CAN SAFELY DISCONTINUE IMMUNOSUPPRESSION
- THE AVAILABILTY OF A SENSITIVE AND SPECIFIC NON-INVASIVE TEST TO DETECT THE POTENTIAL FOR GRAFT REACTIVITY PRIOR TO GRAFT DYSFUNCTION WOULD FACILITATE THE PROCESS OF INDUCING **COT**