Desensitization Strategies for Heart Transplantation in the Young

Lakshmi R. Gokanapudy Hahn, MD, MSCI

WashU Medicine

Sensitization

- Antibodies to human leukocyte antigens (HLA)
- Antibody strength can be defined by mean fluorescence intensity (MFI) and antibody titer
- Enter unacceptable antigens (center specific MFI cut offs) into UNOS = calculated panel reactive antibody (cPRA)
  - A cPRA of 50% → 50% of donors would be unacceptable
  - Higher the cPRA, the harder it is to find an acceptable donor

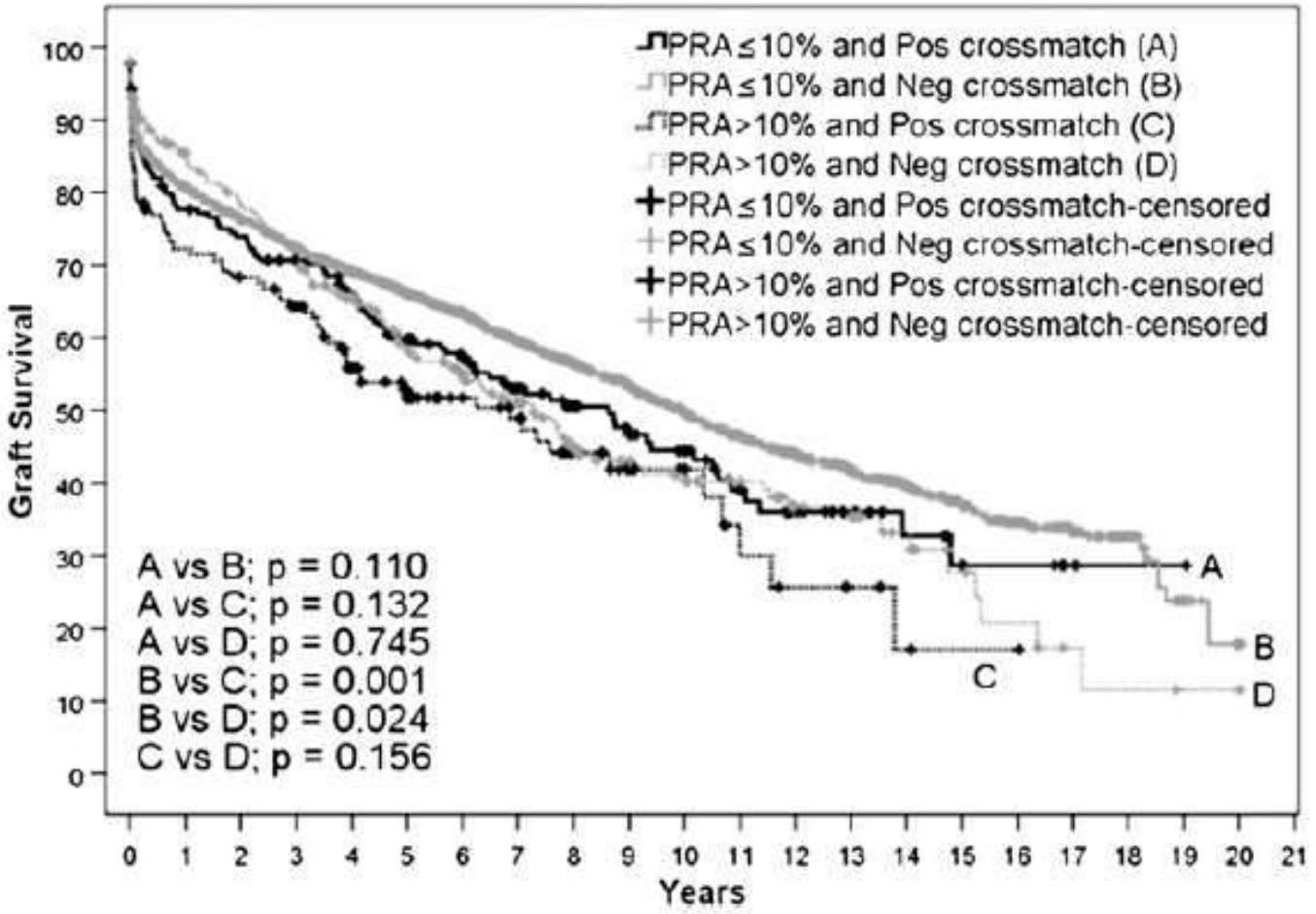
Pediatric patients

- Distinct from adult transplant candidates, pediatric candidates are
  - i) more likely to have congenital heart disease, where exposure to bypass and homograft during prior palliative procedures markedly increases the risk of sensitization, and
  - ii) less likely to benefit from long-term durable support
- Desensitization strategies, however are used rarely and have unclear efficacy
- No standardized management protocols for desensitization in Pediatric Heart Transplant exist to date

Sensitization in PHT

- Prevalence of sensitization (PRA > 10%): 11% - 21%
- SRTR: PRA > 20% increased from 15.5% to 28.2% in pediatric patients from 2005-2015

- **Patients at risk for high PRA**:
  - Multiple transfusions
  - Multiple surgeries
  - Retransplant patients
  - Homografts
  - Mechanical support
- **Outcomes:**
  - Increased waiting times
  - Reduced patient survival
  - Increased CMR
  - Increased AMR
  - Increased CAV



Rossano, J Thorac Cardiovac Surg 2010; 140:694

High PRA and PHT outcomes

- **CTOT (2017)**: PHT across a +XM, in sensitized patients (MFI > 1000) was associated with acceptable first year graft and patient survival, although AMR rates were high and correlated with higher DSA strength

- **PHTS (2023):** 9.5% of transplants were performed across a +XM. No significant difference was noted in 10-year survival between the +XM vs. -XM groups, however, a **cPRA > 50%** in the +XM group emerged as a significant risk factor for graft loss

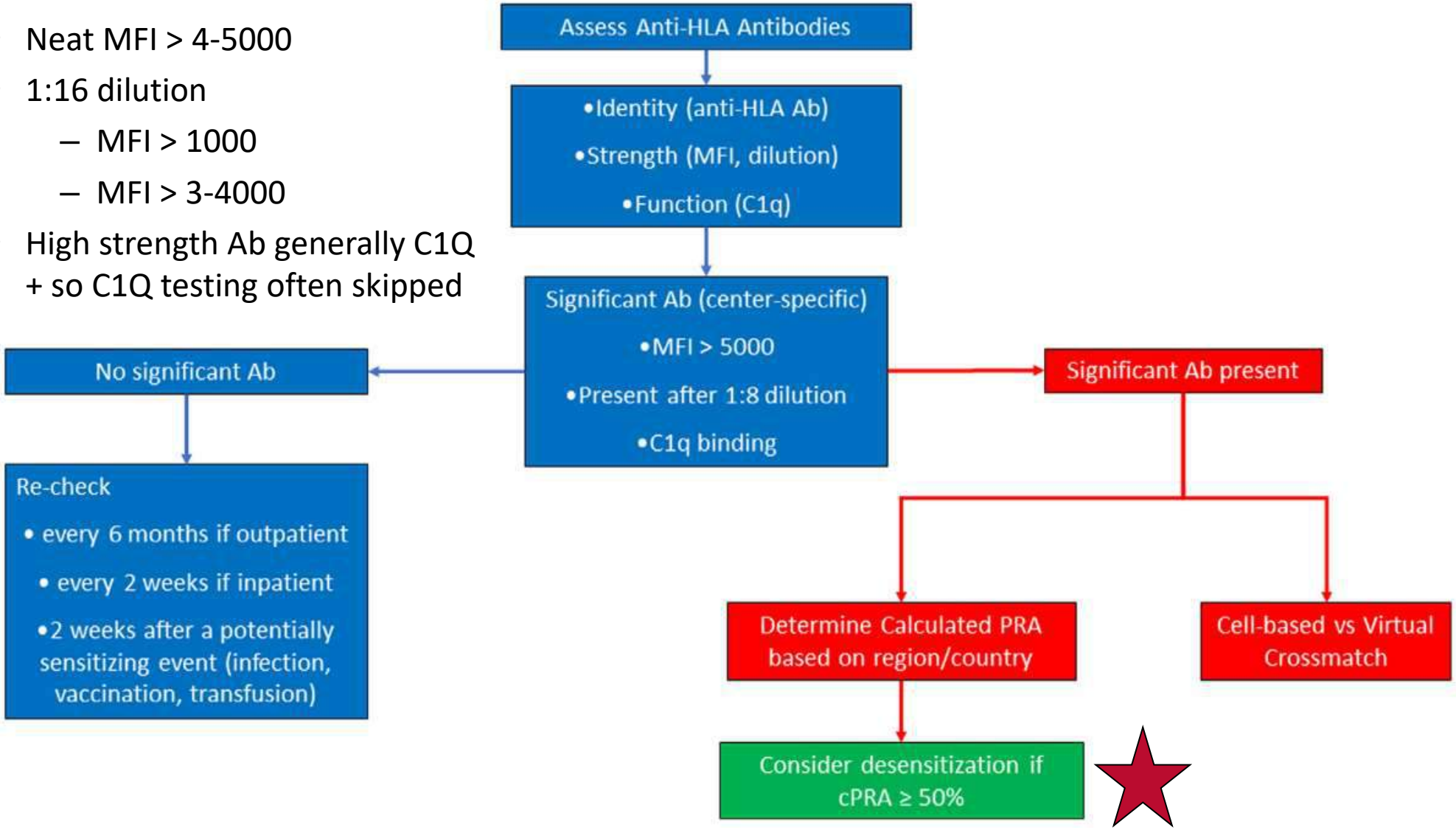
- **UNOS (2023)**: 1 year mortality (nearly 30%, a 4-fold increase) and graft loss were higher in highly sensitized (**cPRA > 80%**) pediatric patients compared to nonsensitized patients, and +XM was also associated with increased risk of mortality and graft loss

Questions to consider:

- Who should undergo desensitization?
- What are the best methods for detecting antibody and how frequently should they be monitored?
- What is the best therapy or management strategy for desensitization?
- What are the goals of desensitization?

What is an unacceptable antigen?

- Neat MFI > 4-5000
- 1:16 dilution
  - MFI > 1000
  - MFI > 3-4000
- High strength Ab generally C1Q + so C1Q testing often skipped



DeFilippis et al, JHLT 2023; 42:409

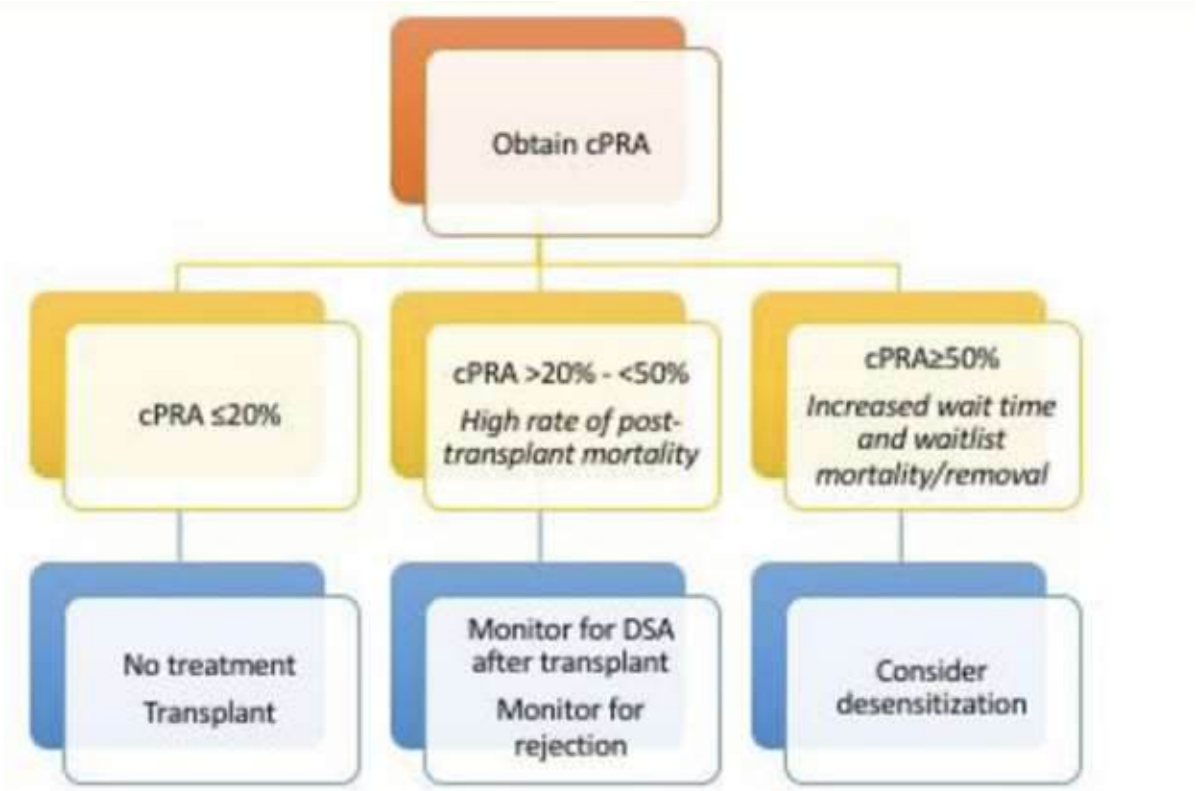
AHA SCIENTIFIC STATEMENT

Sensitization in Heart Transplantation: Emerging Knowledge: A Scientific Statement From the American Heart Association

Monica M. Colvin, MD, MS, FAHA, Chair, Jennifer L. Cook, MD, FAHA, Vice Chair, Patricia P. Chang, MD, MHS, Daphne T. Hsu, MD, FAHA, Michael S. Kiernan, MD, MSc, FAHA, Jon A. Kobashigawa, MD, FAHA, JoAnn Lindenfeld, MD, FAHA, S. Carolina Masri, MD, Dylan V. Miller, MD, E. Rene Rodriguez, MD, Dolly B. Tyan, PhD, and Adriana Zeevi, PhD On behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Cardiovascular Surgery and Anesthesia

When to desensitize?

What are the goals of desensitization?



Contemporary outcomes of pediatric cardiac transplantation with a positive retrospective crossmatch

Irene D. Lytrivi[1] | Devin Koehl[2] | Paul Esteso[3] | Erik L. Frandsen[4] | Meredith K. Gibbons[1] | James K. Kirklin[2,5] | Ryan Cantor[2] | Jacqueline M. Lamour[6] |

Patient characteristics	+ XM group (n = 373)	− XM group (n = 3541)	p-value
Age (y) at transplant	6.9 ± 5.9	7.0 ± 6.3	.76
Age group (y)			<.0001
<1 year	79 (21.2%)	1049 (29.6%)	
1–5 years	103 (27.6%)	702 (19.8%)	
5–10 years	66 (17.7%)	483 (13.6%)	
10–15 years	74 (19.8%)	720 (20.3%)	
>15 years	51 (13.7%)	587 (16.6%)	
PRA > 10%	223 (63.5%)	750 (22.8%)	<.0001
PRA > 50%	153 (43.6%)	230 (7.0%)	<.0001
Listing status			.77
Priority	346 (92.8%)	3270 (92.3%)	
Routine	27 (7.2%)	271 (7.7%)	
Time on Waitlist (months)	5.6 ± 9.1	4.7 ± 8.9	.06
Ventilator	58 (15.8%)	537 (15.3%)	.81
ICU	185 (56.7)	1672 (55.2%)	.78
VAD	113 (30.3%)	983 (27.8%)	
ECMO	12 (3.2%)	136 (3.8%)	
CPB Time (min)	199.1 ± 108.1	175.9 ± 77.9	<.0001
Donor Ischemic Time (min)	228.2 ± 70.3	217.4 ± 73.1	.007
Induction Therapy	344 (92.2%)	3044 (86.1%)	.0009
Treatment for elevated PRA	90 (25.3%)	70 (1.98%)	<.0001

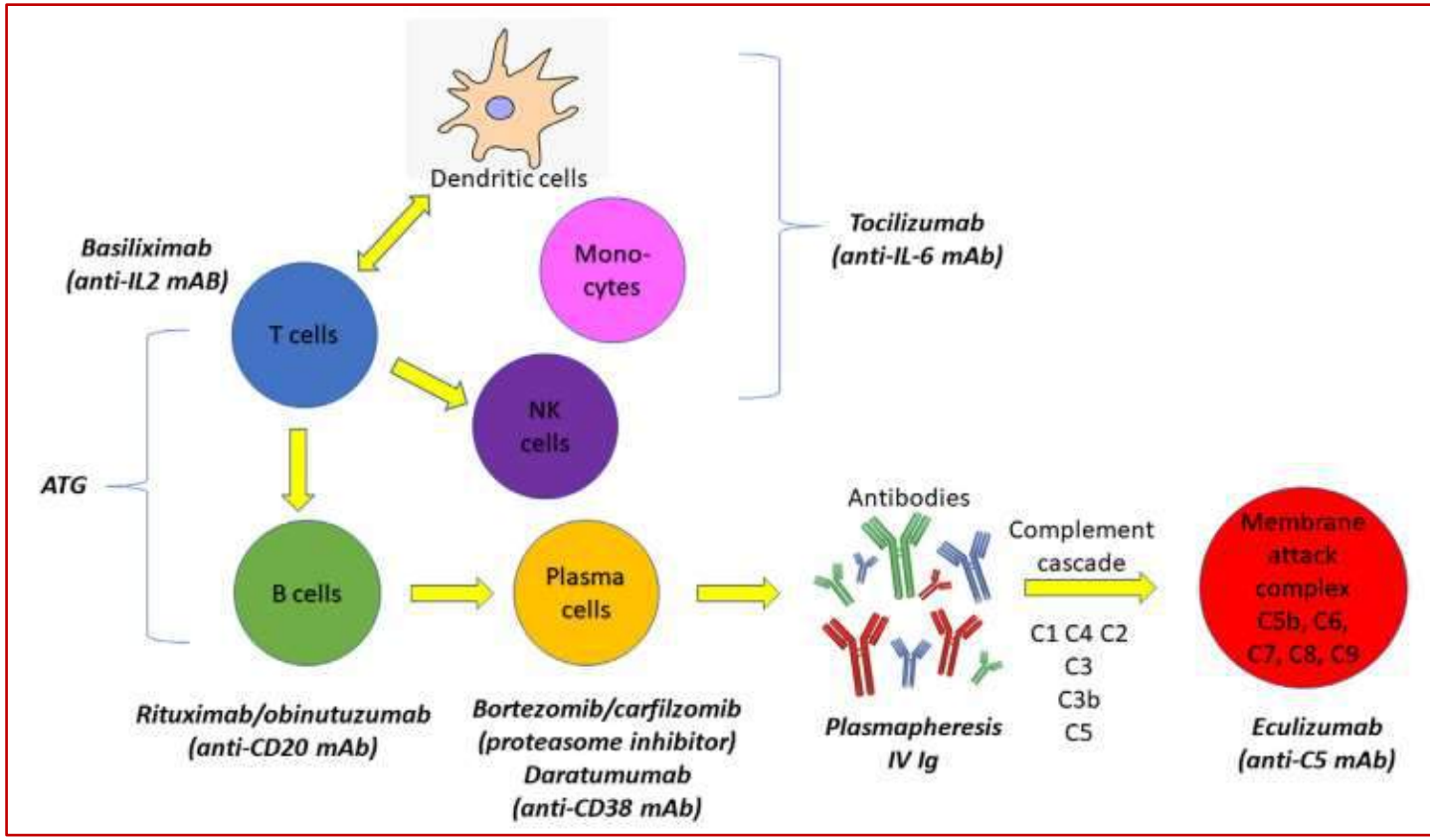
Desensitizing the pediatric transplant candidate

- Desensitization: 4% of the cohort.
- 24.1% of +XM, 2% of –XM
- **Most common therapies**:
  - Rituximab: 41.1%
  - IVIG: 33.3%
  - Plasmapheresis: 28.9%
  - Bortezomib: 8.9%
  - Prophylactic plasma exchange intra operatively: 52.3%

Risk Factors for All Patients (n = 3914)				
Variable	HR	95% Lower CI	95% Upper CI	p-value
African American	1.4	1.1	1.7	.0004
Congenital Heart Disease	2.0	1.6	2.4	<.0001
Induction Therapy	0.8	0.6	1.0	.03
ECMO at Transplant	2.4	1.7	3.2	<.0001
VAD at Transplant	1.2	1.0	1.5	.03
PRA > 50% at Listing	1.3	1.0	1.6	.04
Positive XM	1.0	0.8	1.4	.63

Desensitization strategies

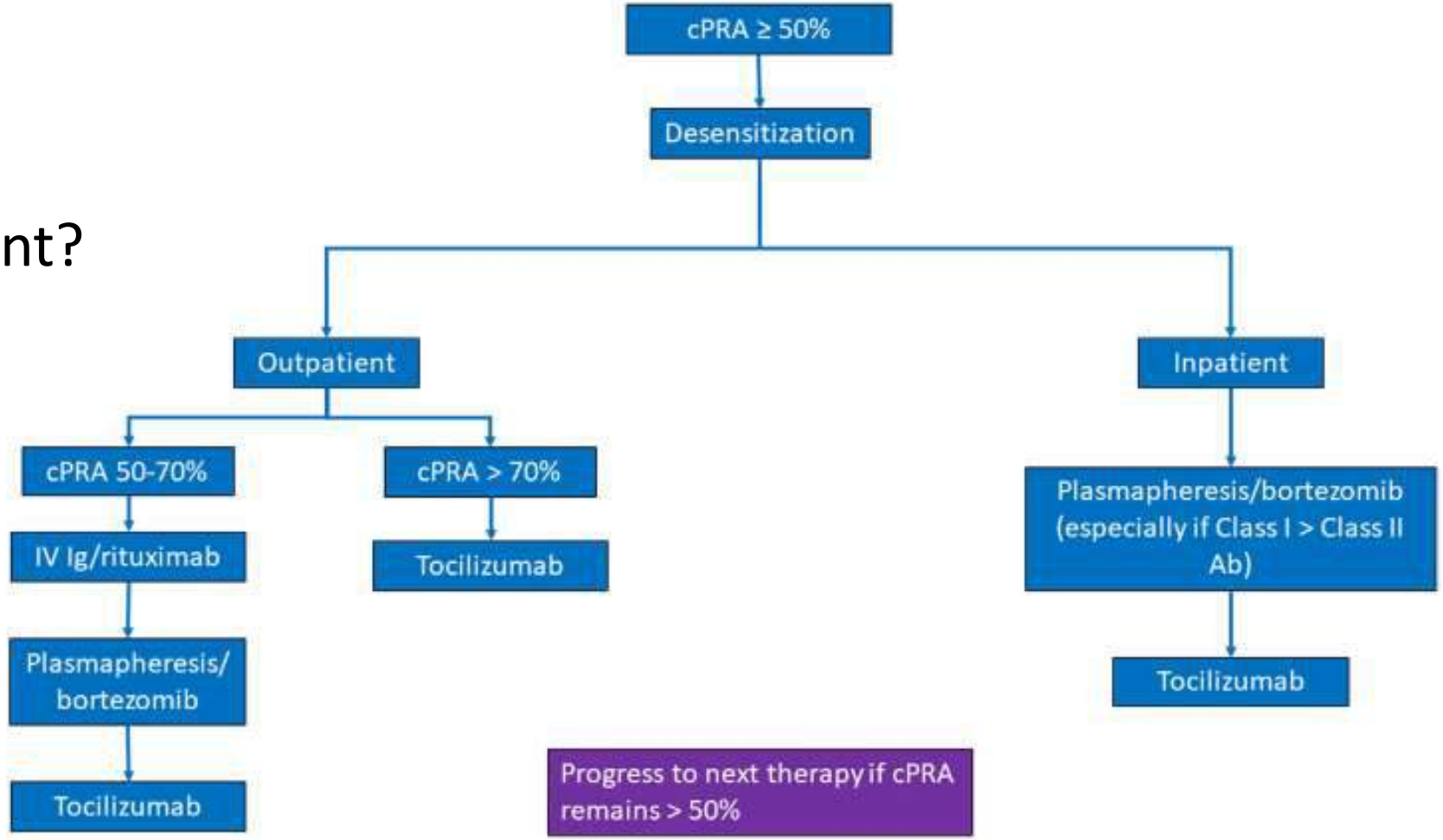
Inactivation	IVIG
Removal	Plasmapheresis
Decreased production	Rituximab, Bortezomib



DeFilippis et al, JHLT 2023; 42:409

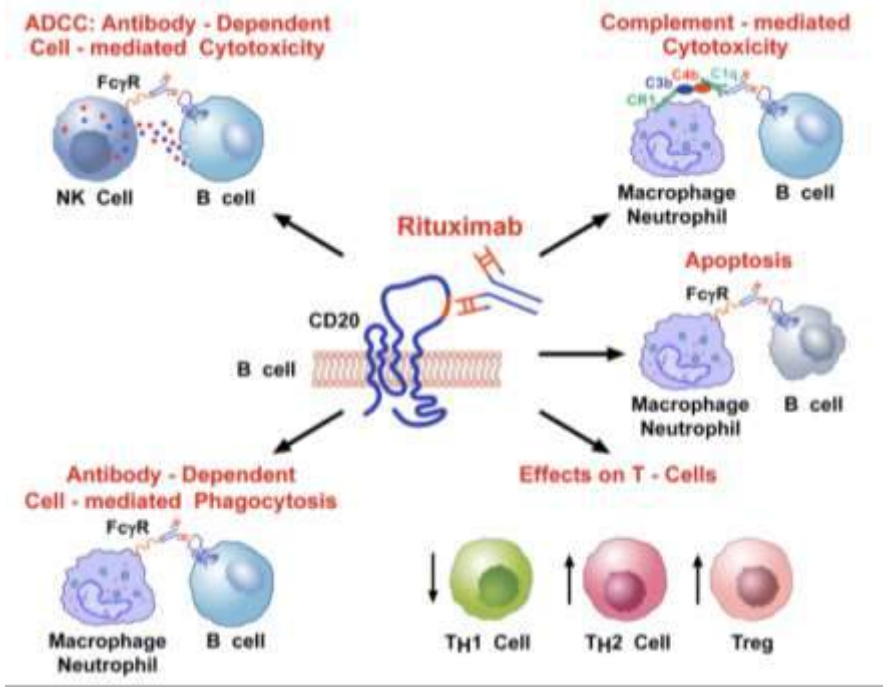
Desensitization strategies

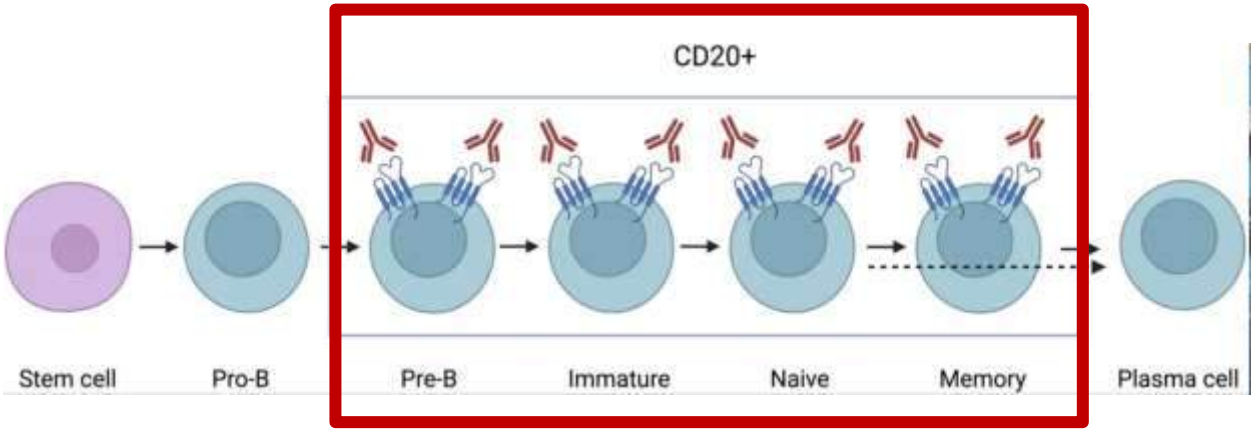
- Which drug/strategy?
- Inpatient vs. Outpatient?
- Duration of therapy?



DeFilippis et al, JHLT 2023; 42:409

B cell targeting strategies: Rituximab





HOWEVER:

Limited ability to adequately suppress HLA Ab responses

1. Does not prevent denovo DSA
2. CD20 Ag is absent on B cell precursors and antibody secreting plasmablasts/ plasma cells
3. Incompletely eliminates CD27+ memory B cells

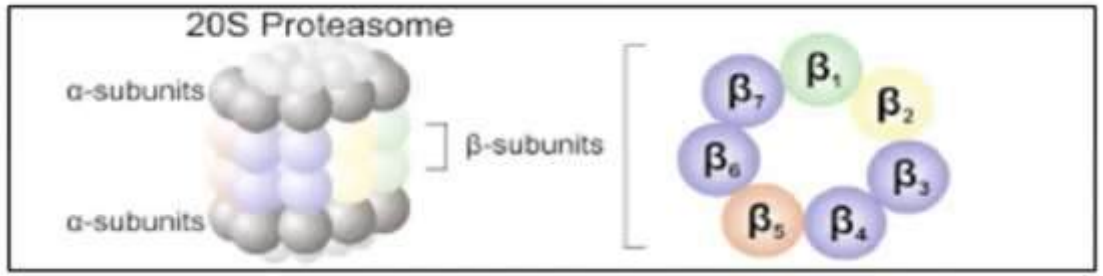
- **Patel et al**: successful desensitization of 4 sensitized heart transplant candidates with Rituximab and IVIG.
- **Schumacher et al**: 14 heart transplant candidates, 8 were responders and 5 were transplanted. Treatment with IVIG and Rituximab increased donor pool from 10% to 85% among responders

Importance of Cellular Microenvironment and Circulatory Dynamics in B Cell Immunotherapy[1]

Qian Gong,* Qinglin Ou,* Shiming Ye,* Wyne P. Lee,* Jennine Cornelius,[§] Lauri Diehl,*[§] Wei Yu Lin,* Zhilan Hu,* Yanmei Lu,[‡] Yongmei Chen,[†] Yan Wu,*[†] Y. Gloria Meng,[‡] Peter Gribling,* Zhonghua Lin,* Kathy Nguyen,* Thanhvien Tran,* Yifan Zhang,* Hugh Rosen,[¶] Flavius Martin,* and Andrew C. Chan[2]*

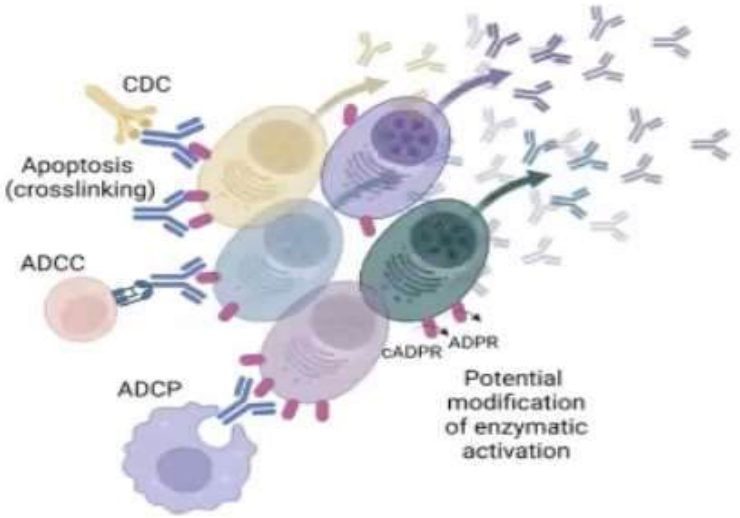
Plasma cell targeting strategies

Proteosome inhibitors



e.g. Carfilzomib

Anti-CD38

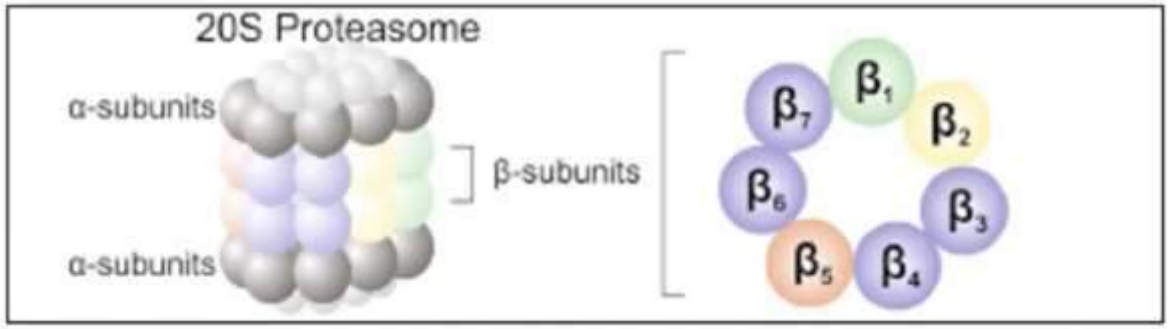


e.g. Daratumumab

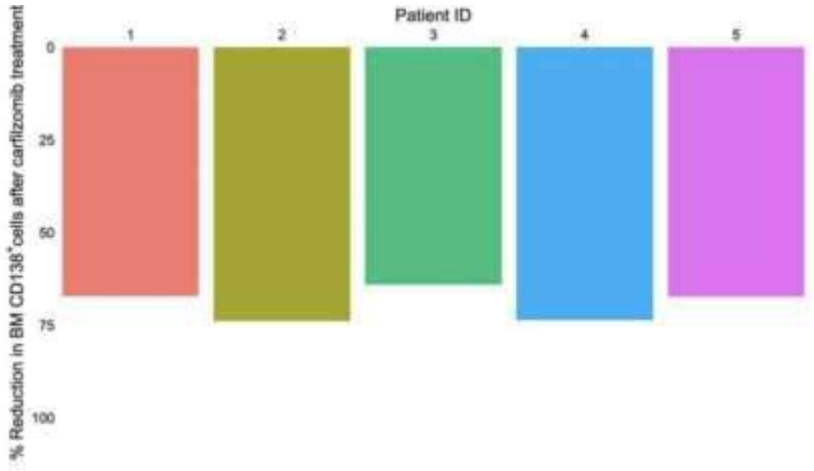
Proteosome Inhibitors
Carfilzomib

Vs. Bortezomib:

- Better in vitro cytotoxicity
- Clinical superiority to bortezomib in relapsing/refractory multiple myeloma
- Effect is dose dependent
  - Dosing range in myeloma: 20 mg/m^2 to 72 mg/m^2 IV



Moderate dose carfilzomib reduces CD138+ bone marrow plasma cells in sensitized patients by ~69%



Select potential Risks/Benefits:

- Cardiotoxicity
- Hypertension (including PHTN)
- AKI
- Hepatotoxicity
- Less neuropathy

Tremblay S, et al. A prospective, iterative, adaptive trial of carfilzomib-based desensitization. Am J Transplant. 2020 Feb;20(2):411-421. doi: 10.1111/ajt.15613.

Thanks to Dr. Habal for this slide.

ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Impact of carfilzomib-based desensitization on heart transplantation of sensitized candidates

Roy Sriwattanakomen, MD,[a,1] Qingyong Xu, PhD,[b,1] Moses Demehin, PharmD,[c] Michael A. Shullo, PharmD,[d] Massimo Mangiola, PhD,[b] Gavin W. Hickey, MD,[e] Christopher M. Sciortino, MD, PhD,[f] Edward T. Horn, PharmD,[g] Mary E. Keebler, MD,[e,2] and Adriana Zeevi, PhD[b,2]

Clinical Protocol:

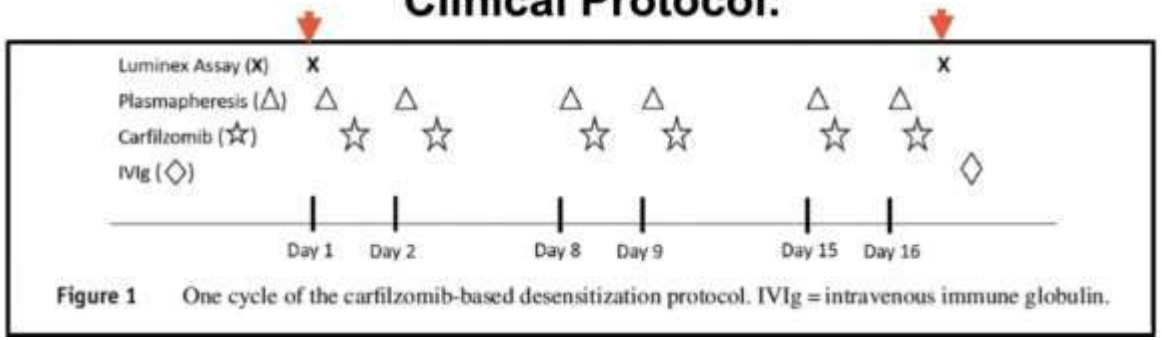


Figure 1 One cycle of the carfilzomib-based desensitization protocol. IVIg = intravenous immune globulin.

Neat cPRA:
- Class I significantly reduced
- Minimal impact on class II

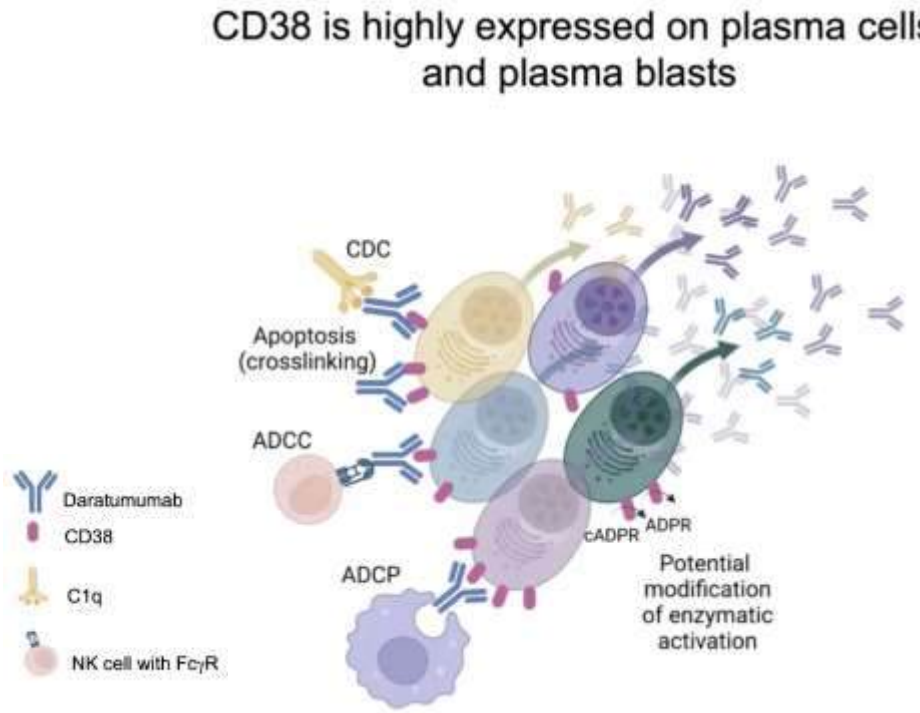
Dilutions and C1q cPRA
- More accurately reflected change in higher titer antibodies.

Transplanted:
- 5/6 on LVAD
- 100% survival

Delisted/died:
- Homograft
- Renal transplant
- Multiparous/LVAD

Thanks to Dr. Habal for this slide.

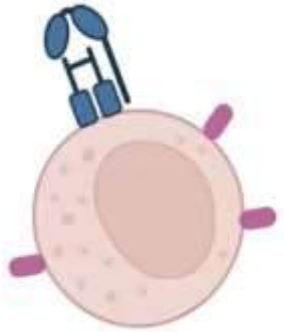
CD38 targeted therapies to reduce plasma cells



Daratumumab:

- Used in multiple myeloma alone (3rd line) and in combination with a proteasome inhibitor (1st line).
- No cardiotoxicity or neurotoxicity.

- Depletes bone marrow plasma cells through pleiotropic mechanisms
- Daratumumab with plerixafor significantly reduced DSA in a non-human primate model
- CD38 is expressed on NK cells



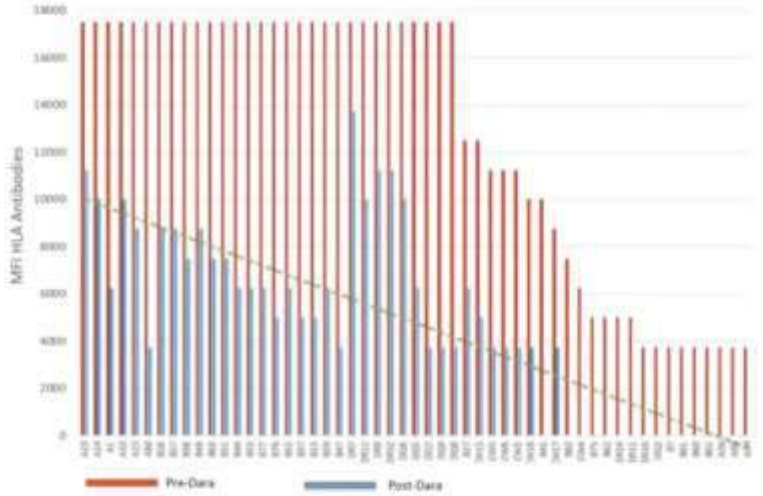
Potential adjunctive benefits to prevent early AMR?

Thanks to Dr. Habal for this slide.

Daratumumab in sensitized heart transplant candidates: case reports

Case 1: Treatment refractory, highly sensitized heart transplant candidate.

- Dara x 4 weeks reduced class I and II cPRA.

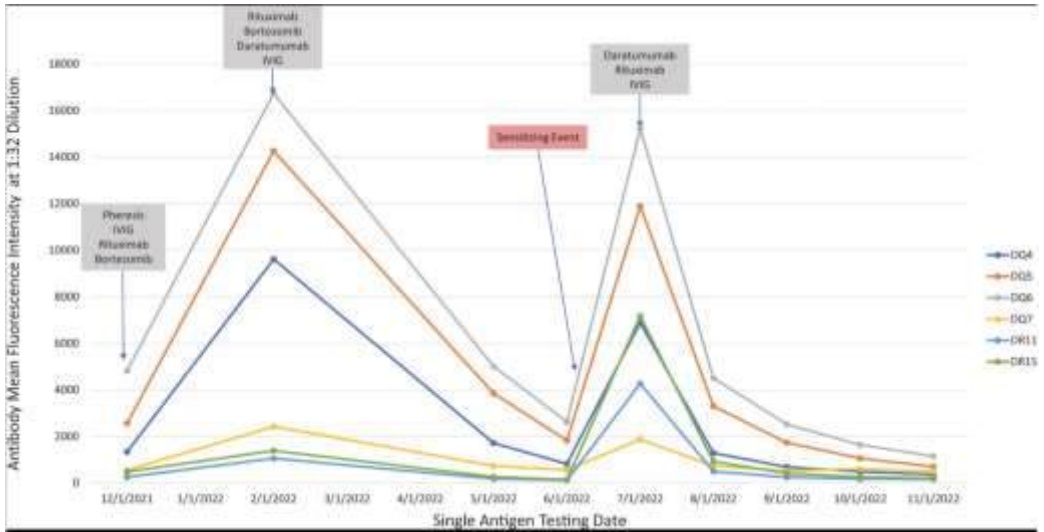


(Jordan et al., ATC 2020)

Case 2: 62F highly sensitized despite multiple rounds of pheresis, IVIG, rituximab.

- cPRA increased after plasmapheresis alone then decreased (98% to 62%) after daratumumab.
- Transplanted across 2 previously unacceptable DSA.

(Kwun et al., JASN 2019)



New Desensitization Strategy: Daratumumab for Highly Sensitized Pediatric Heart Transplant Candidate

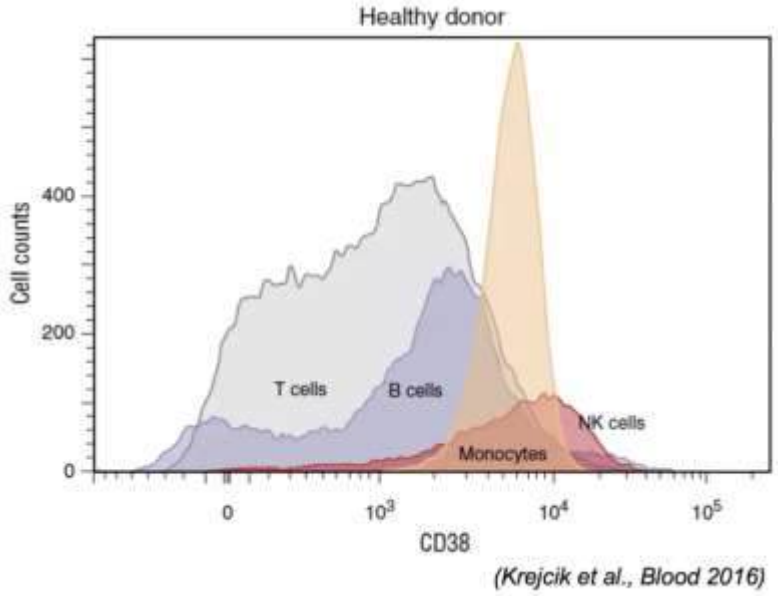
Baez Hernandez, Nathanya MD[1,2]; Butts, Ryan MD[1,2]; Radel, Laura MD[1,2]; Bano, Maria MD[1,2]; Lantz, Jodie CNS[1,2]; Davies, Ryan MD[1,2,3]; Lacelle, Chantale PhD[4]; Iqbal, Mehreen MD[1,2]; Ellimuttil, Tracey PharmD[5]

Author Information

Transplantation 107(10):p e271-e272, October 2023. | **DOI:** 10.1097/TP.0000000000004719

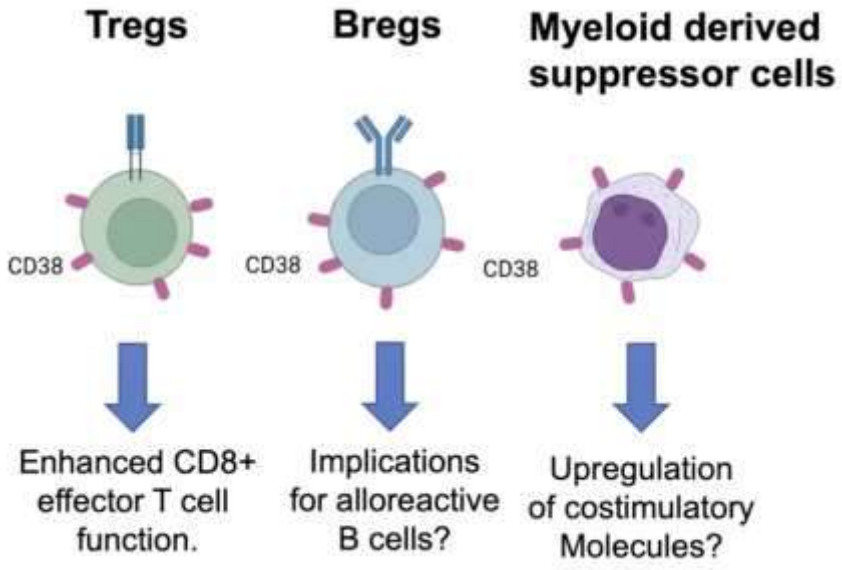
CD38 is widely expressed

CD38 is widely expressed on various cell lineages.



(Krejcik et al., Blood 2016)

Including regulatory cells.



In the non-human primate model, despite effective desensitization, the animals developed TCMR and DSA rebound.

Thanks to Dr. Habal for this slide.

Implications for transplant?

- Use of dara to treat kidney ABMR: case reports of TCMR and DSA rebound.
  - Jordan et al., ATC 2020
  - Doberer et al., Transplantation 2021

- Recent case report, of steroid resistant TCMR early post transplant in a low-immunological risk kidney transplant recipient receiving maintenance Dara for multiple myeloma.
  - Scalzo et al. Am J Kidney Disease 2023

Thanks to Dr. Habal for this slide.

Challenges and looking to the future

- Variability in etiology and degree of sensitization
- Lack of standardization across HLA labs
- Lack of standardization of sensitization “cut offs” meriting desensitization
- Deficits in our understanding of the factors driving memory B cell and plasma cell differentiation, persistence and resistance to desensitization
- Does desensitization alter long term outcomes?

AHA/Enduring Hearts Translational Research Award in PHT: 2024-2028

Contemporary Approach to Desensitization: CFZ/BELA

PI: Gokanapudy Hahn, WashU/SLCH

Core Labs: HLA: Zeevi, UPMC;
Mechanistic: Habal, NYU; DCC: PHTS

Clinical sites: SLCH (Canter), CHOP (Rossano), BCH (Daly), CHOA (Mao), CHOC (Simpson), NYPMSCH (Zuckerman)

Study

- A prospective, multicenter, observational study of a dual immunotherapy approach for desensitization that will combine an intensive proteosome inhibitor (PI) Carfilzomib (CFZ) based regimen with costimulatory blockade with Belatacept (BELA).
- This strategy is **novel** in PHT patients and we hypothesize that it will substantially enhance our ability to transplant ***highly sensitized (cPRA$_{MFI>4000}$ ≥ 50%)*** pediatric/ young adult patients.

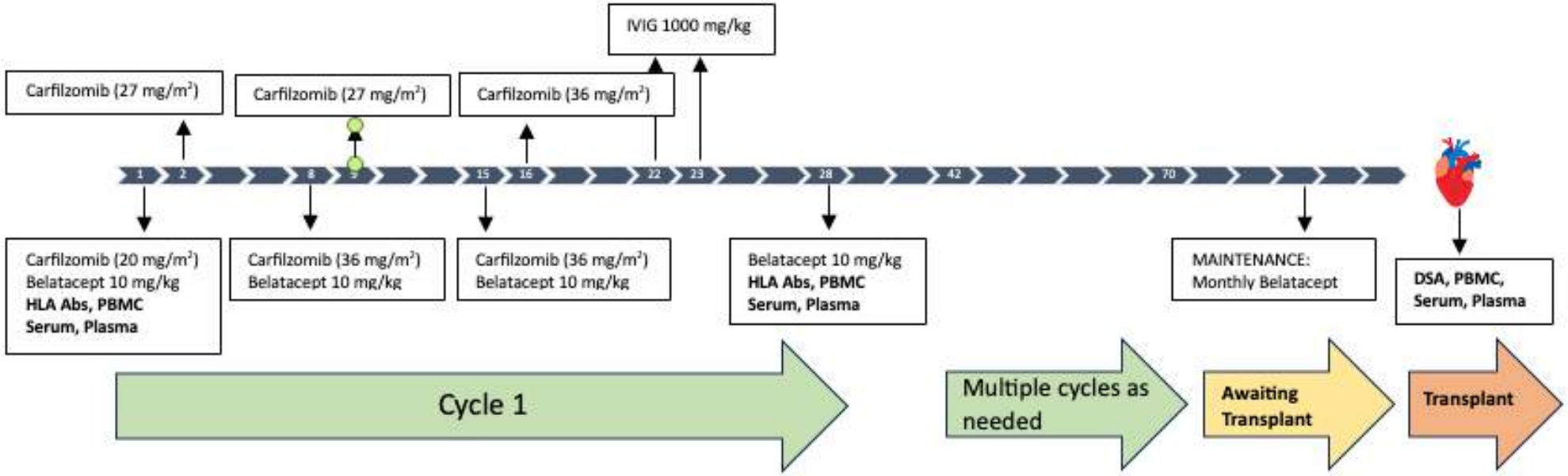


Figure 1: Desensitization Protocol using a combination of Carfilzomib and Belatacept. Human Leukocyte Antigen antibodies (HLA Abs); Peripheral blood mononuclear cells (PBMCs)

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