Immunologically high-risk kidney transplantation - the role of desensitization protocols

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What are the key challenges in kidney transplantation today?

- **Shortage of organs worldwide**
- **Improving long-term graft survival**
- **Searching for the most appropriate graft for each recipient**
- **Optimizing the ischemia time**
- **Minimizing the impact of surgery and subsequent immunosuppressive therapy**
- **Transplantation of highly sensitized patients**

Vázquez-Martul D et al. Archivos Españoles de Urología 2021;74(10): 1058-1065

Definition of sensitization

HLA antibodies are termed donor-specific (DSA) if they recognize HLA proteins found in the allograft, or non-DSA if the HLA antigens are not present on the transplanted organ

- **Development of antibodies to the human leukocyte antigens (HLA) - HLA antibodies** (prior to or after transplantation)

  - associated with transplant rejection, graft dysfunction and poor overall survival

  - HLA sensitization can result from any exposure to HLA (previous blood transfusions, pregnancies or transplants)

The strongest connection is with a history of prior transplantation (43 of 75 candidates for re-transplantation (57%) were sensitized) *

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Abbes S et al. Ther Apher Dial. 2017; 21(5): 441–450.
* Duquesnoy RJ, et al. Transplant immunology. 2008;18(4):352.

Detection of HLA antibodies – measurement the degree of sensitization

HLA incompatible transplantation (HLAi) is defined by a positive CDC or FCM crossmatch.

- **CDC crossmatch detects only complement-activating HLA-antibodies**
- **Flow Cytometric crossmatch (FCM) detects the non-complement fixing IgG subclasses (IgG2, IgG4)**

* antibodies detected in FCM - more a risk factor than a contra-indication for transplantation

Single antigen beads (SAB) - Luminex

- **More sensitive than CDC and FCM for detecting HLA antibodies and DSA**
- **The degree of antibody is expressed as mean fluorescence intensity (MFI)**
- **Significant MFI of 1,000–1,500 (there is no general agreement on this value)**

vPRA (virtual PRA) **cPRA (calculated PRA)** **cRF (calculated reaction frequency)**

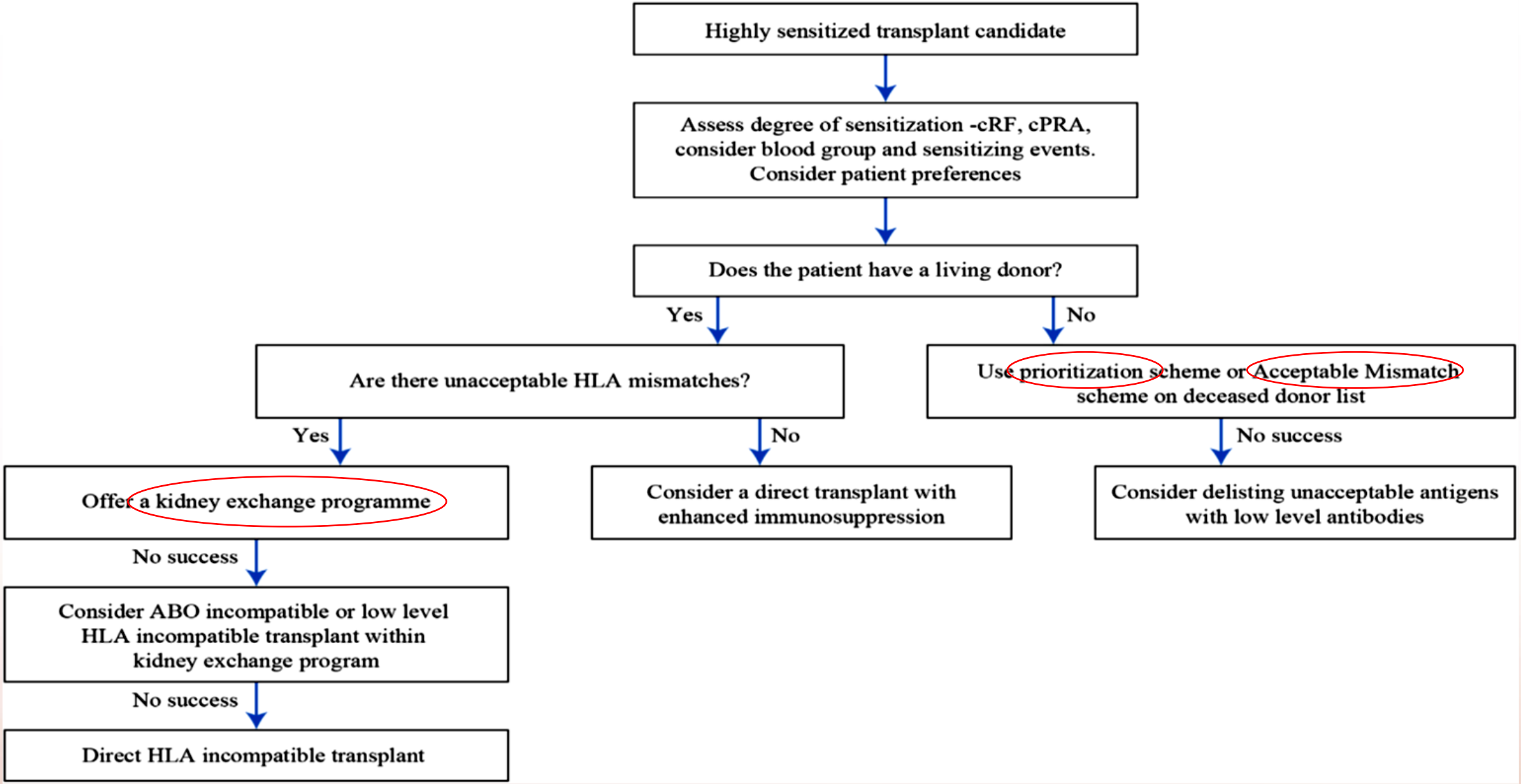
estimate the chance that a patient has HLA antibodies reactive with a donor from the actual organ donor population

Pandey P, et al. J Immunoassay Immunochemistry.2021;42:300–13.
Huber L, et al. Transpl Int. 2015;28:710–9.
Cecka JM.. Am J Transpl.2010;10:26–9.

Improvement in transplantation and technology

- **The improvement of techniques to detect anti-HLA antibodies in recipients waiting for kidney transplantation has allowed us to detect a larger number of sensitized patients.**
- **In Spain in a period 2010-2015 number of recipients waiting for kidney with PRA >75% increased from 20% to 50%.**
- **With the growing number of candidates for retransplantation, 35% of patients awaiting a renal transplant are sensitized.**

Heidt S, et al. Kidney Int. 2018;93:491–500.
UNOS. United Network for Organ Sharing. http://www.unos.org. Updated 2017.



Algorithm of options for a highly sensitized transplant candidate

European Society of Organ Transplantation (ESOT) working group, Transplant International 2022.

United Network of Organ Sharing (UNOS)

- **implemented a new deceased donor kidney allocation system (KAS) in 2014 in the United States**
- **increased the allocation priority for sensitized candidates on waiting list**
- **patients with a cPRA 80-84% received 2.5 allocation points**
- **patients with a cPRA ≥ 99.5% received 202 allocation points**

Reports have shown that it has been very effective for highly sensitized patients (≥99.5% cPRA), but very highly sensitized patients (ex. >99.9%) continue to be transplanted at a low rate.

Zhou S, Massie AB, Luo X, et al. Am J Transplant. 2018;18:1415-1423.
Stewart DE, et al.Am J Transplant. 2016;16:1834-1847.

Schinstock CA, et al. Clin Transpl. 2019; 33:e13751

USA, Waiting list on June 1, 2016.

Sensitized candidates (cPRA ≥ 80%) were younger, more likely female, more likely to be on dialysis, on dialysis for a longer period of time, and more likely to have had a prior transplant than candidates with a cPRA < 80% ($p < 0.001$).

Outcomes of the "100%" cPRA candidate

- **5.5% (3233) candidates on the active list had a cPRA of 100%**
  - **16.3% received a transplant during 1-year follow-up**
  - **6.6% were removed from the waitlist**
  - **4.3% died**
  - **17.1% were made temporarily inactive**

Schinstock CA, et al. Clin Transpl. 2019; 33:e13751

Are the desensitization protocols needed today (in the era of kidney exchange programs)**?**

Despite having a high priority on waiting list, highly sensitized patients rarely receive a kidney transplant against which they do not have DSAs and consequently require transplantation across the HLA barrier.

Studies' suggest that:

- **Outcomes of DSA-positive transplants are comparable to DSA negative patients**
- **Patients who receive an HLA incompatible kidney transplant after desensitization have an improved survival compared with comparable candidates who remain on dialysis**

Heidt S, et al. Transpl Immunol 2015; 33:51.
Orandi BJ, et al. Am J Transplant. 2014;14:1573-1580.
Schinstock CA, et al. Transplantation. 2017;101:2429-2439.
Orandi BJ, et al. N Engl J Med. 2016;375:288-289.

Are the desensitization protocols needed today (in the era of kidney exchange programs)**?**

- **candidates with a cPRA > 99.9% may benefit from desensitization, take into account**
  - blood type (B or O)
  - wait-list mortality
  - potential removal from the list
  - candidate age
- **candidates with an approved HLA incompatible living donor, desensitization is a reasonable because it offers**
  - the benefits of getting a living donor transplant
  - an avoidance of wait-list morbidity and mortality
  - dialysis can be avoided

Schinstock CA, et al. Clin Transpl. 2019; 33:e13751

ESOT | Transplant International

GUIDELINES
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European Guideline for the Management of Kidney Transplant Patients With HLA Antibodies: By the European Society for Organ Transplantation Working Group

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The most efficacious desensitization strategy is to start with rounds of plasma exchanges/immunoadsorption together with IVIG or B-cell depletion with anti-CD20 monoclonal antibodies (1C).

Desensitization protocols

STANDARD OF CARE

- **plasmapheresis or immunoadsorption,**

followed by IVIg (low- dose, 100 mg/kg, or high- dose, 2 g/kg)

Montgomery, R. A. & Zachary, A. Pediatr. Transplant. 2004; 8, 535–542.
Bohmig, G. A. et al. Am. J. Transplant.. 2007; 7, 117–121.

Desensitization protocols

- **anti-CD20 antibodies (Rituximab) and high-dose IVIgs (2 g/kg over 2–4 days)**

*anti- CD20 alone does not have proven efficacy for reducing DSA

*new anti-CD20 monoclonal antibodies (such as ocrelizumab or obinutuzumab) may be more efficient

Vo AA, Lukovsky M,, et al. N Engl J Med. 2008; 359:242–51.

- **proteasome inhibitors (decrease the synthesis of proteins (DSAs)) – bortezomib, carfilzomib, ixazomib**

*monotherapy is ineffective, in combination with standard of-care antibody reduction therapy

*bortezomib is indicated for multiple myeloma, the mechanism of action of these drugs is the disruption of the normal intracellular protein degradation process

Woodle ES, et al. Am J Transpl. 2015; 15:101–18.
Everly, M. J. et al. Transplantation. 2008; 86, 1754–1761.

Desensitization protocols

- **anti-C5 monoclonal antibody (Eculizumab)**

***** DSAs not fixing the complement

Marks WH, et al. Am J Transpl. 2019; 19:2876–88.

- **C1-inhibitor**

- subject of clinical trials (theoretical advantage compared with eculizumab is that C1-inhibitor blocks the complement pathway more proximally and therefore prevents the formation of anaphylatoxins and activation of innate immunity)

Berger M, et al. Transplantation. 2019; 103:1763–75.

Desensitization protocols

- **cysteine protease** (IG endopeptidase, Ides, Imlifidase and Idefirix®)

*Imlifidase is currently the only approved therapy for use in the EU for desensitization treatment of highly sensitized adult kidney transplant patients with a positive crossmatch against an available deceased donor. It cleaves all IgGs without regard to their specificity, with an immediate action that lasts around 5–7 days; this drug cannot be re-dosed due to immunogenicity

Kjellman C, et al. Am J Transpl. 2021; 21:3907–18.

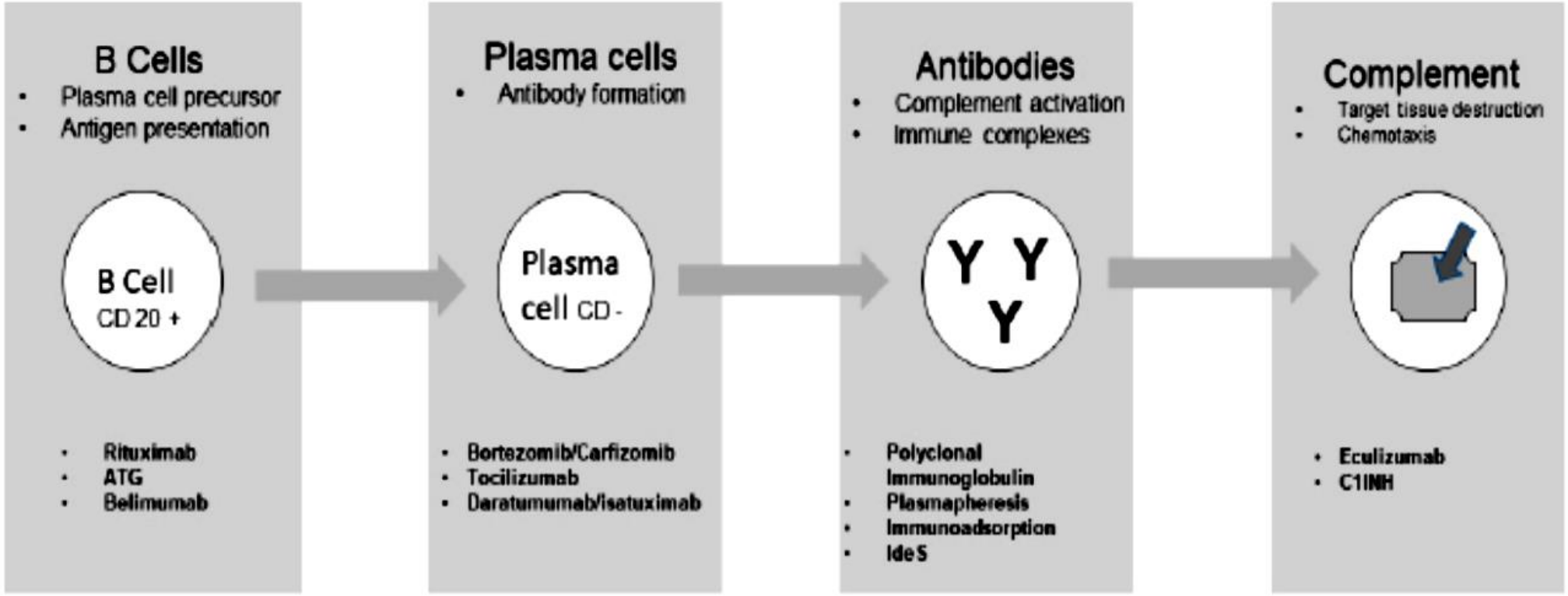
- **anti-IL6 receptor monoclonal antibody (Tocilizumab)**

***has been successfully used in combination with high- dose IVIg and anti- CD20 to desensitize patients who failed standard of-care desensitization therapy

- **Belimumab (anti BAFF)**

Choi J, et al. Am J Transpl. 2017; 17:2381–9.
Banham GD, et al. The Lancet. 2018; 391: 2619–30.

Summarized



Targeting different cells or functions

Salvadori M. Transplantology 2023; 4(3), 139-150

Timing of Desensitization

-used in Austria

-immunoadsorption followed with ATG and/or Rituximab

-graft survival rates at 3 years are similar in CDCXM-positive and negative patients

1. the immediate pre-transplant desensitization
2. the post-transplant desensitization

- used at the Necker Hospital in Paris (started in 2002)

- induction therapy (ATG), followed by high-dose IVIg that is repeated every 3 weeks for a total of four courses; 5-10 plasmapheresis; at the end of plasmapheresis, 1 or 2 Rituximab

- 95 patients, MFI > 3000, 7-year allograft survival rate was 78%

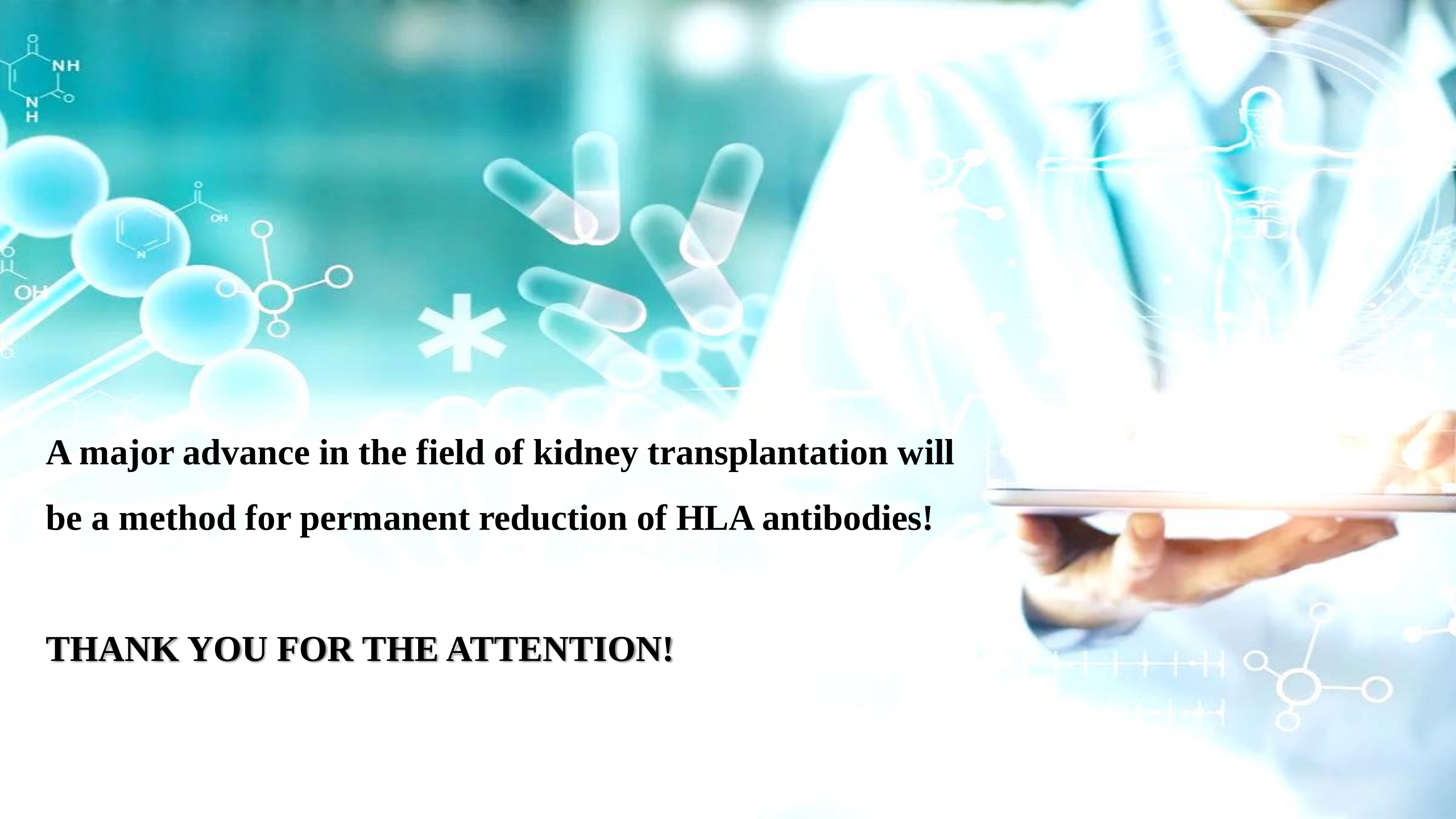
Schwaiger, E et al.Nephrol. Dial. Transplant. 2016; 31, 1342–1351.
Amrouche, L et al. Transplantation 2017; 101, 2440–2448.

Candidates for Desensitization

- **Study suggests that even a mild reduction in cPRA would markedly increase the rate of transplantation.**

All kidney transplant candidates with CPRA > 99.9%
Kidney transplant candidates with CPRA > 98% with HLA incompatible approved living donor who has not received a transplant after 1 y in KPD
Kidney transplant candidates with CPRA > 98% and >5 y of waiting time

Schinstock CA, et al. Clin Transpl. 2019; 33:e13751



A major advance in the field of kidney transplantation will be a method for permanent reduction of HLA antibodies!

THANK YOU FOR THE ATTENTION!