transplantology

MDPI

Editorial

Strategies for Access to Kidney Transplantation for Highly Sensitized and Incompatible Patients

Maurizio Salvadori

Department of Renal Transplantation, Careggi University Hospital, Viale Pieraccini 18, 50139 Florence, Italy; maurizio.salvadori1@gmail.com; Tel.: +39-055-597151

One of the major challenges in developing programs for kidney transplantation is represented by the presence of antibodies targeting the HLA of the donor in the recipients and, in particular cases, the incompatibility of the ABO blood groups among donor and recipient for living donors. This Editorial to the Special Issue "Strategies for Access to Kidney Transplantation for Highly Sensitized and Incompatible Patients" aims to clarify the problem and to describe the principal strategies to overcome it.

Hum oral memory

The humoral alloimmune memory represents the main barrier for transplant tolerance [1,2]. Previous transplants, transfusions and pregnancies may be responsible for such memory. The main assays to detect serological and cellular humoral HLA sensitization include complement-dependent cytotoxicity, flow cytometry, ELISA and single-antigen bead complement binding [3].

The graft survival rates between HLA-incompatible (HLAi) and HLA-compatible (HLAc) kidney transplants dramatically differ in large cohorts in both the USA [4] and in Europe [5]. The ABO incompatibility that often limits living donor transplantation represents a particular aspect of graft survival.

Strategies used in immune patients

The principal strategies used in highly immunized patients to ensure a safe kidney transplantation are desensitization, evaluating the priority points in deceased-donor kidney-allocation programs, living donor kidney paired exchange programs and acceptable mismatch programs.

Desensitization

In the case of living donation, desensitization may be attempted as an early pretransplant desensitization or as an immediate pretransplant desensitization. Post-transplant desensitization may be principally used in the case of deceased donors [6].

Several drugs either old (high-dose intravenous immunoglobulins) or new or in clinical trials are used in desensitization as described by a review from Jordan et al. [7]. As shown in Figure 1, the targets of these drugs are B cells, plasma cells, antibodies and complement. Drugs against B cells such as rituximab (RTX), anti-T-cells immunoglobulins (ATG) and belimumab. Belimumab inhibits the growth and differentiation of B cells by blocking B lymphocyte stimulator (BAFF or BlyS). Belimumab monotherapy was studied as a desensitization agent in kidney transplantation, but the study was terminated early for lack of efficacy. Later, the efficacy of belimumab was documented in a randomized, placebo-controlled study [8].

Drugs against plasma cells are represented by proteasome inhibitors, such as bortezomib or carfilzomib [9,10], anti-IL-6 antibodies, such as Clazakizumab [11], and anti-CD38 antibodies, such as daraturumab [12]. Techniques to remove antibodies include plasmapheresis or immunoadsorption or IgG endopeptidase [13]. Finally, anti-complement

Citation: Salvadori, M. Strategies for Access to Kidney Transplantation for Highly Sensitized and Incompatible Patients. *Transplantology* **2023**, *4*, 85–89. https://doi.org/10.3390/transplantology4020009

Received: 10 May 2023
Accepted: 12 May 2023
Published: 22 May 2023

drugs, such as eculizumab, have been documented for their efficacy [14,15]. Other anti-complement drugs are represented by C1 inhibitors (serine protease inhibitors) such as Cinryze, Berinert and Ruconest. These drugs are not yet used as prophylaxis treatments, but preliminary positive results for antibody-mediated rejection have been obtained [16].

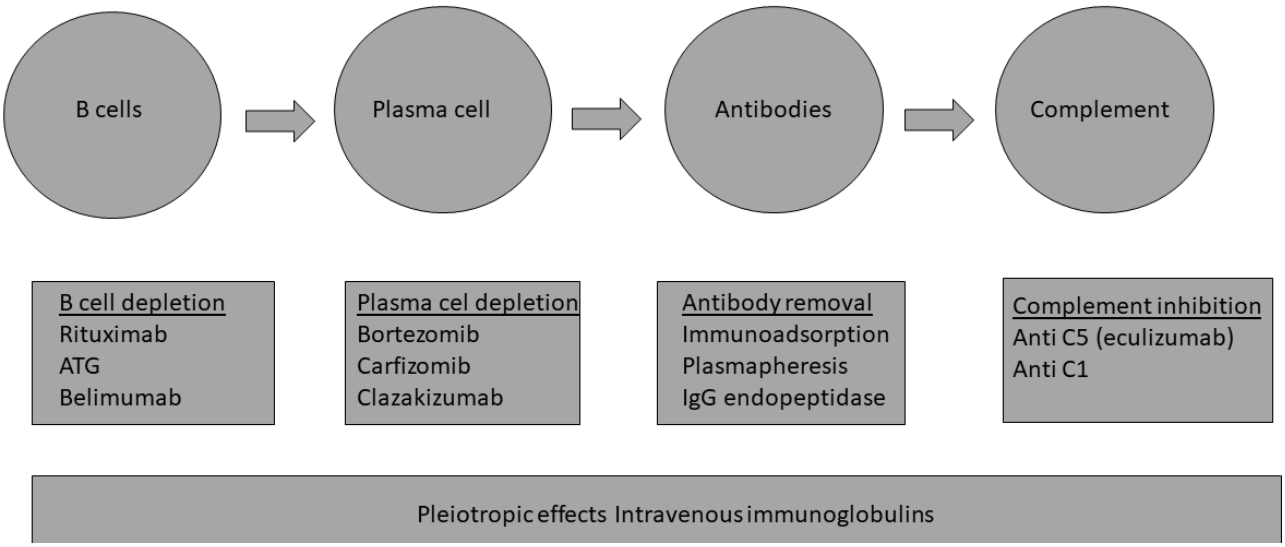

Figure 1. Available options to therapeutically intervene on B-cell immunity.

In addition or independently from desensitization, there are several strategies for highly sensitized patients to obtain easier access to the HLAc kidney transplant program.

Priority points in deceased-donor kidney allocation programs

These priority points are based on the following:

- PRA was calculated to evaluate the unacceptable HLA antigens using the "virtual cross-match".
- A sliding scale score from low but positive cPRA (>20%) to the highest cPRA (100%) was developed.
- Local to regional or national kidney organs allocation were prioritized.
- The best organs were given to the best recipients.
- ABO compatible rather than identical organs were allocated.

The USA kidney allocation system implemented these points in 2014 and 1 year after this implementation, the high immune transplant rates increased from 2.4% to 13.4% with a reduction in mean waiting time; however, very highly immunized patients still remained waitlisted [17].

Living-donor kidney-paired exchange programs

These programs are based on the increased acceptable HLAAg repertoire and take advantage that long-term KPD may be distinguished by cross-matching, due to unacceptable antigens and include ABOi pairs to achieve HLAc kidney transplantation.

The number of KPDs is growing more and more (Figure 2) and there are several types of KPD: (A) two incompatible pairs swap kidneys in a two-way exchange; (B) a three-way exchange with no reciprocal exchanges so that hard-to-match pairs are better matched; (C) in a list exchange, an incompatible donor donates to a wait-list candidate in exchange for wait-list priority for the recipient; (D) DPD pairs an altruistic donor with an incompatible recipient and then the donor continues the chain or donates to a wait-listed candidate; and (E) a compatible pair can join an exchange that helps hard-to-match pairs [18].

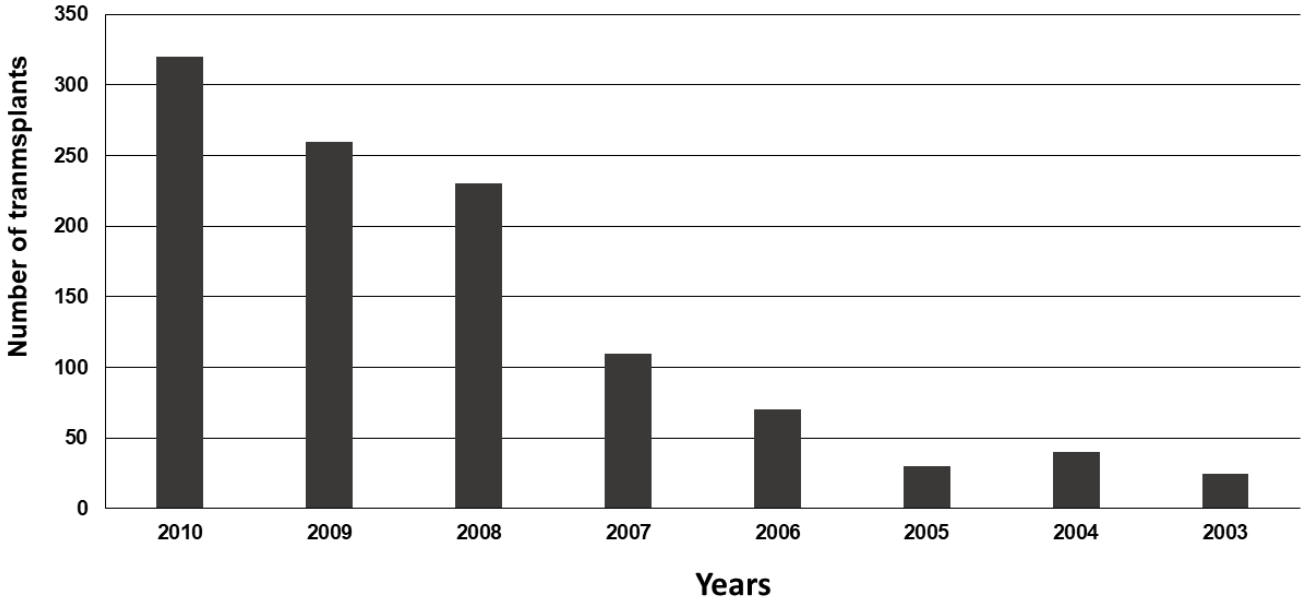

Figure 2. Kidney paired donations in the USA, 2003–2010.

Acceptable mismatch programs

These programs are not based on the prevention of mismatches, but on facilitating the access to transplantation through the identification of acceptable antigens, i.e., the HLA antigens to which the recipient has no antibodies against.

The Eurotransplant Acceptable Mismatch (AM) program was initiated more than 25 years ago to facilitate transplantations for highly sensitized renal transplant candidates. Patients enrolled in the program should have the following characteristics: a CDC-PRA >85% with respect to the blood donors; a single-antigen bead (SAB) assay verification based on previous immunization events should be performed; ABO group must be compatible; and a minimal HLA MM Criteria (MMC) should consists of 2/1 DR loci plus 1 B locus [19]. Observing the 10-year graft survival rate and comparing the match effect of HLA antigen mismatches, no effect of HLA antigen mismatches was observed for patients within the AM program, whereas for patients receiving a kidney transplant outside the AM program, a match effect for HLA antigen mismatches was observed by Kaplan–Meier curves analysis [20,21].

Overall, these data demonstrate that highly sensitized patients are well served by receiving a compatible organ based on AM [22].

The EUROSTAM project is the extension of the Eurotransplant Acceptable Mismatch Program in other European regions to increase access to transplantation for HS patients.

A simulation performed by five European laboratories (Eurotransplant, UK, Spain, Greece, Prague) in patients with a cPRA > 95% and 5 years on a waiting list, showed that the chance of finding a compatible donor increased by 27% by expanding the donor pool in Europe.

The following are the final recommendations:

- Define the humoral risk in kidney transplants; the use of the ENGAGE 5 strata system is recommended;
- Implement strategies to maximize the access to HLA-compatible transplantation:
    - Sliding scale priority score programs for the very HS groups (cPRA > 98%);
    - Expand the living-donor kidney exchange programs (LDKEP) (including low-risk ABOi donors) and develop tools to help assess the probability of an organ match;
    - Expand the AM Program to more European countries;

- Prioritization policies should be linked across countries for equity of access;
- However, a number of HS candidates will never find a compatible donor and would need to undergo desensitization to receive a transplant

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Torija, A.; Favà, A.; Meneghini, M.; Crespo, E.; Bestard, O. Novel insights into the pathobiology of humoral alloimmune memory in kidney transplantation. *Curr. Opin. Organ. Transplant.* **2020**, *25*, 15–21. [CrossRef] [PubMed]
2. Chong, A.S. New insights into the development of B cell responses: Implications for solid organ transplantation. *Hum. Immunol.* **2019**, *80*, 378–384. [CrossRef] [PubMed]
3. Bestard, O.; Couzi, L.; Crespo, M.; Kessaris, N.; Thaunat, O. Stratifying the humoral risk of candidates to a solid organ transplantation: A proposal of the ENGAGE working group. *Transpl. Int.* **2021**, *34*, 1005–1018. [CrossRef] [PubMed]
4. Orandi, B.J.; Garonzik-Wang, J.M.; Massie, A.B.; Zachary, A.A.; Montgomery, J.R.; Van Arendonk, K.J.; Stegall, M.D.; Jordan, S.C.; Oberholzer, J.; Dunn, T.B.; et al. Quantifying the risk of incompatible kidney transplantation: A multicenter study. *Am. J. Transplant.* **2014**, *14*, 1573–1580. [CrossRef]
5. Manook, M.; Koeser, L.; Ahmed, Z.; Robb, M.; Johnson, R.; Shaw, O.; Kessaris, N.; Dorling, A.; Mamode, N. Post-listing survival for highly sensitised patients on the UK kidney transplant waiting list: A matched cohort analysis. *Lancet* **2017**, *389*, 727–734. [CrossRef]
6. Amrouche, L.; Aubert, O.; Suberbielle, C.; Rabant, M.; Van Huyen, J.D.; Martinez, F.; Sberro-Soussan, R.; Scemla, A.; Tinel, C.; Snanoudj, R.; et al. Long-term Outcomes of Kidney Transplantation in Patients with High Levels of Preformed DSA: The Necker High-Risk Transplant Program. *Transplantation* **2017**, *101*, 2440–2448. [CrossRef]
7. Jordan, S.C.; Ammerman, N.; Choi, J.; Huang, E.; Peng, A.; Sethi, S.; Najjar, R.; Toyoda, M.; Lim, K.; Louie, S.; et al. Novel Therapeutic Approaches to Allosensitization and Antibody-mediated Rejection. *Transplantation* **2019**, *103*, 262–272. [CrossRef]
8. Banham, G.D.; Flint, S.M.; Torpey, N.; Lyons, P.A.; Shanahan, D.N.; Gibson, A.; Watson, C.J.E.; O'Sullivan, A.M.; Chadwick, J.A.; Foster, K.E.; et al. Belimumab in kidney transplantation: An experimental medicine, randomised, placebo-controlled phase 2 trial. *Lancet* **2018**, *391*, 2619–2630. [CrossRef]
9. Diwan, T.S.; Raghavaiah, S.; Burns, J.M.; Kremers, W.K.; Gloor, J.M.; Stegall, M.D. The impact of proteasome inhibition on alloantibody-producing plasma cells in vivo. *Transplantation* **2011**, *91*, 536–541. [CrossRef]
10. Eskandary, F.; Regele, H.; Baumann, L.; Bond, G.; Kozakowski, N.; Wahrmann, M.; Hidalgo, L.G.; Haslacher, H.; Kaltenecker, C.C.; Aretin, M.B.; et al. A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection. *J. Am. Soc. Nephrol.* **2018**, *29*, 591–605. [CrossRef]
11. Doberer, K.; Duerr, M.; Halloran, P.F.; Eskandary, F.; Budde, K.; Regele, H.; Reeve, J.; Borski, A.; Kozakowski, N.; Reindl-Schwaighofer, R.; et al. A Randomized Clinical Trial of Anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection. *J. Am. Soc. Nephrol.* **2021**, *32*, 708–722. [CrossRef] [PubMed]
12. Kwun, J.; Matignon, M.; Manook, M.; Guendouz, S.; Audard, V.; Kheav, D.; Poullot, E.; Gautreau, C.; Ezekian, B.; Bodez, D.; et al. Daratumumab in Sensitized Kidney Transplantation: Potentials and Limitations of Experimental and Clinical Use. *J. Am. Soc. Nephrol.* **2019**, *30*, 1206–1219. [CrossRef] [PubMed]
13. Jordan, S.C.; Lorant, T.; Choi, J.; Kjellman, C.; Winstedt, L.; Bengtsson, M.; Zhang, X.; Eich, T.; Toyoda, M.; Eriksson, B.M.; et al. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. *N. Engl. J. Med.* **2017**, *377*, 442–453. [CrossRef]
14. Cornell, L.D.; Schinstock, C.A.; Gandhi, M.J.; Kremers, W.K.; Stegall, M.D. Positive crossmatch kidney transplant recipients treated with eculizumab: Outcomes beyond 1 year. *Am. J. Transplant.* **2015**, *15*, 1293–1302. [CrossRef]
15. Marks, W.H.; Mamode, N.; Montgomery, R.A.; Stegall, M.D.; Ratner, L.E.; Cornell, L.D.; Rowshani, A.T.; Colvin, R.B.; Dain, B.; Boice, J.A.; et al. Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: A randomized trial. *Am. J. Transplant.* **2019**, *19*, 2876–2888. [CrossRef] [PubMed]
16. Morgan, B.P.; Harris, C.L. Complement, a target for therapy in inflammatory and degenerative diseases. *Nat. Rev. Drug. Discov.* **2015**, *14*, 857–877. [CrossRef]
17. Stewart, D.E.; Kucheryavaya, A.Y.; Klassen, D.K.; Turgeon, N.A.; Formica, R.N.; Aeder, M.I. Changes in Deceased Donor Kidney Transplantation One Year After KAS Implementation. *Am. J. Transplant.* **2016**, *16*, 1834–1847. [CrossRef]
18. Wallis, C.B.; Samy, K.P.; Roth, A.E.; Rees, M.A. Kidney paired donation. *Nephrol. Dial. Transplant.* **2011**, *26*, 2091–2099. [CrossRef]
19. Claas, F.H.; Witvliet, M.D.; Duquesnoy, R.J.; Persijn, G.G.; Doxiadis, I.I. The acceptable mismatch program as a fast tool for highly sensitized patients awaiting a cadaveric kidney transplantation: Short waiting time and excellent graft outcome. *Transplantation* **2004**, *78*, 190–193. [CrossRef]
20. Heidt, S.; Haasnoot, G.W.; van Rood, J.J.; Witvliet, M.D.; Claas, F.H.J. Kidney allocation based on proven acceptable antigens results in superior graft survival in highly sensitized patients. *Kidney Int.* **2018**, *93*, 491–500. [CrossRef]

21. Heidt, S.; Witvliet, M.D.; Haasnoot, G.W.; Claas, F.H. The 25th anniversary of the Eurotransplant Acceptable Mismatch program for highly sensitized patients. *Transpl. Immunol.* **2015**, *33*, 51–57. [CrossRef] [PubMed]
22. Heidt, S.; Haasnoot, G.W.; van der Linden-van Oevelen, M.J.H.; Claas, F.H.J. Highly Sensitized Patients Are Well Served by Receiving a Compatible Organ Offer Based on Acceptable Mismatches. *Front. Immunol.* **2021**, *12*, 687254. [CrossRef] [PubMed]