



Review

# Update on Desensitization Strategies and Drugs on Hyperimmune Patients for Kidney Transplantation

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**Abstract:** The presence in a recipient of antibodies directed against donor-specific antigens represents a major obstacle to transplantation. Removal of these antibodies represents a challenge for physicians dealing with kidney transplantation. Several strategies, techniques, and old and new drugs are currently used for desensitizing these patients. Desensitization may either occur before transplantation, at the time of transplantation, or after transplantation according to whether physicians are dealing with living or deceased donors. Different techniques may be used to reveal the presence of antibodies in the recipients; each technique has different sensitivities and specificities, and different advantages and drawbacks. The targets of the drugs used to desensitize are B cells, plasma cells, the antibodies themselves, and, finally, the complement that is the final actor causing tissue disruption. B cells are relatively easy to target; targeting the plasma cell is more difficult. Indeed, several new drugs are also used in randomized trials to defeat plasma cells. Antibodies may be removed easily, but their removal is often followed by antibody rebound. The complement is not easy to defeat and new drugs are currently used for this aim. Overall, despite difficulties, desensitization is currently possible in many cases, to obtain a safe and successful transplantation.

**Keywords:** desensitization; donor-specific antibodies; HLA system; antibody identification; B cells; plasma cells; complement



**Citation:** Salvadori, M. Update on Desensitization Strategies and Drugs on Hyperimmune Patients for Kidney Transplantation. *Transplantology* **2023**, *4*, 139–150. <https://doi.org/10.3390/transplantology4030014>

Academic Editor: Gaetano Ciancio

Received: 30 May 2023

Revised: 28 June 2023

Accepted: 2 August 2023

Published: 8 August 2023



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## 1. Introduction

Desensitization is among the different strategies that allow kidney transplantation in highly sensitized and incompatible patients [1]. Indeed, humoral alloimmunity against human leukocyte antigens (HLAs) is one of the major barriers for successful transplantation. A number of B cell subsets drive this immune mechanism even if a number of intimately related B and T cell subsets maintain an effective humoral alloimmune response. These subsets are alloreactive memory B cells (mBC) [2], T follicular helper (TFH) cells, and long-lived plasma cells (LLPC) located in different lymphoid organs.

## 2. Development of Sensitization

After the first alloantigen exposure, events such as pregnancies, transfusions, previous transplants, or any contact with alloimmune antigens may cause a second exposure that generates a memory alloimmunity, both cellular and serological [3,4].

When B cells bind to their cognate antigen, they initiate a migration toward the boundary between the B and T cell zones in lymphoid organs, where they compete for interactions with follicular helper cells. T follicular helper cells provide selection signals required for their differentiation into Germinal Center (GC) cells and into antibody-secreting cells. Additionally, it has been observed that after transplantation, circulating TFH expanded more significantly in patients who developed de novo anti-HLA antibodies than in those who remained not sensitized [5]. An important role in generating an alloimmune response is exerted by the long-lived plasma cells. After the generation of memory B cells, these transform into plasmablasts that are competent for homing into survival niches. Plasmablasts

migrating to bone marrow generate long-lived plasma cells. The latter, under the effect of pathogen-associated molecular patterns (PAMPs), migrate to survival niches [6,7]. Most of the plasmablasts migrate to inflamed tissues, under the control of the interferon-gamma-induced expression of CXC-chemokine receptor 3 (CXCR3), which binds CXC-chemokine ligand 9 (CXCL9), CXCL10, and CXCL11 [8,9].

### 3. Techniques to Identify Sensitization Level and to Stratify the Risk

With different techniques, it is now possible to detect both the alloreactive serological memory and the alloreactive cellular memory in patients waiting for kidney transplantation. Through this approach, it is now possible to stratify the humoral and cellular risk of a candidate to receive a specific solid organ transplantation [10].

The serological memory may be detected using complement-dependent cytotoxicity [11], flow cytometry [12], solid-phase assays such as ELISA [13], and bead-based assays such as Luminex [14]. All these assays are shown in Table 1. On the other hand, assays to evaluate alloreactive cellular memory are, among others, flow cytometry [15], Elispot assay [16], solid-phase assay [17], and flow cytometry [18].

**Table 1.** Available assays evaluating alloreactive serological memory.

Method	Antigen Detection System	Advantages	Limitations
Complement-dependent cytotoxicity [11]	Donor lymphocytes Rabbit complement	PPV+++ of hyperacute rejection	Low sensitivity for low-level antibodies FP may be caused by non-HLA or auto-antibodies
Flow cytometry [12]	Donor lymphocytes Fluorescently labeled antibody to T/B cells and to IgG	More sensitive than CDC Detects low-level DSA Predictive of early AMR	Positivity may be due to nonspecific antibody confirmed by a positive auto-XM In absence of DSA by SAB, a positive FC XM is not predictive of reaction
ELISA [13]	HLA molecules from platelet donors or EBV-transformed cells on a microtiter plate	First assays to use captured HLA proteins, enabling testing without donor cells	Low sensitivity and specificity
Bead-based assays on Luminex [14]	HLA-purified antigen on plastic beads Fluorescently labeled antibody to IgG. Beads can have a mix or individual HLA (SAB)	More sensitivity and specificity than CDC and FC in sensitized patients Less FP than ELISA, especially for class II antibody	Interpretation requires expertise Significant variations between laboratories and kits FP reactions for denatured conformation of HLA on bead surface not correlated with AMR

AMR, antigen-mediated reaction; CDC, complement-dependent cytotoxicity; DSA, donor-specific antibody; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; FC, flow cytometry; FP, false positive; HLA, human leukocyte antigen; Ig, immunoglobulin; PPV, positive predictive value; SAB, single-antigen bead; XM, crossmatch.

The immune-pathophysiology of DSA-mediated damages may cause antibody-mediated rejection and graft loss. The pathogenicity of DSAs is routinely evaluated by their titer (MFI or dilution) or their ability to bind donor cells (by flow cytometry crossmatch). Ex vivo complement binding can be evaluated with the C1q and/or C3d assays. Analysis of complement-fixing IgG subclasses or complement genetic variations, the number of innate immune effectors, and the polymorphism of Fcγ receptors could all help achieve a better stratification of the risk for antibody-mediated rejection (AMR). Measurement of DSA affinity and glycosylation profile is not yet available. Finally, the characteristics of the target graft endothelial cell (level of expression of HLA molecules, stress-induced ligands, or expression

level of complement regulators or cytoprotective proteins) influence the pathogenicity of the DSA.

All the cited assays for detecting the presence of HLA sensitization have different sensitivities and specificities. CDC has the lowest sensitivity. Sensitivity increases with the use of flow cytometry and a further increase is reached with the use of ELISA. The optimal sensitivity and sensibility are obtained through the use of single beads and complement binding. This fact allows for realizing the ENGAGE's proposal for categorization of the humoral risk of solid-organ transplant categories. The European Guidelines for the Management of Graft Recipients (ENGAGE) [10] is an initiative from the European Society for Organ Transplantation that stratify the patient's risk as follows:

- (a) If the patient has no DSA and no cellular memory, the transplant is possible with a low risk for AMR;
- (b) If at the time of transplantation, there is an absence of DSAs but there is a potential cellular memory against the donor HLA, the transplant is possible with an increased risk for AMR. The cellular memory is possible if there are historical DSAs and/or pregnancy or a previous transplant with repeat antigens. Other possibilities are transfusions with no information on blood donors.
- (c) If at the time of transplantation, there are DSAs, but with negative flow, the transplant is possible with a risk for acute AMR and acceptable medium-term graft survival.
- (d) If at the time of transplantation, there are DSAs with positive flow and negative CDC, the transplant is possible, but there is a very high risk for acute AMR and accelerated chronic AMR.
- (e) If at the time of transplantation, there are DSAs with positive CDC, the transplant is not possible and there is the need of desensitization before proceeding with the transplant.

#### 4. Incidence of Hyperimmune Patients and Graft Survival with Desensitization

The number of hyperimmune patients on the waiting list for kidney transplantation is increasing with time and with the technique used. According to Spanish data of 2020, the proportion of sensitized patients with CDC-PRA > 50% ranged from 10% to 15%, but the same patients evaluated by PRA-SAB (single antigen beads) increased to 40–50% [19].

In the USA, according to data from Montgomery et al. [20], more than 20,000 candidates for kidney transplant are sensitized. The authors conducted a study with desensitization on 211 sensitized patients and found that patient survival rates were 80.6% at 8 years from transplantation, as compared with 30.5% for patients that remained on the waiting list. In a different multicenter study on the risk of incompatible kidney transplantation, Orandi et al. [21] compared the graft survival of patients with positive Luminex and negative flow cross match (PLNC) with positive flow and negative CDC (PFNC) and patients with positive CDC (PCC). All these patients were compared with compatible transplants. The hazard ratio (HR) for graft loss was 1.20 for PLNC, 1.65 for PFNC, and 1.80 for PCC. The graft loss for the last two groups was significant ( $p < 0.001$ ). In a different study conducted in the UK, Manook et al. [22] compared hyperimmune patients desensitized before transplantation with compatible living donors (CLDs) and compatible deceased donors (CDDs). The 5-year graft survival rates were similar and the authors concluded that desensitization has no detrimental influence on patient survival rates even if it does not offer a survival benefit.

#### 5. Timing of Desensitization

Considering the day of transplantation, different timing and strategies may be applied.

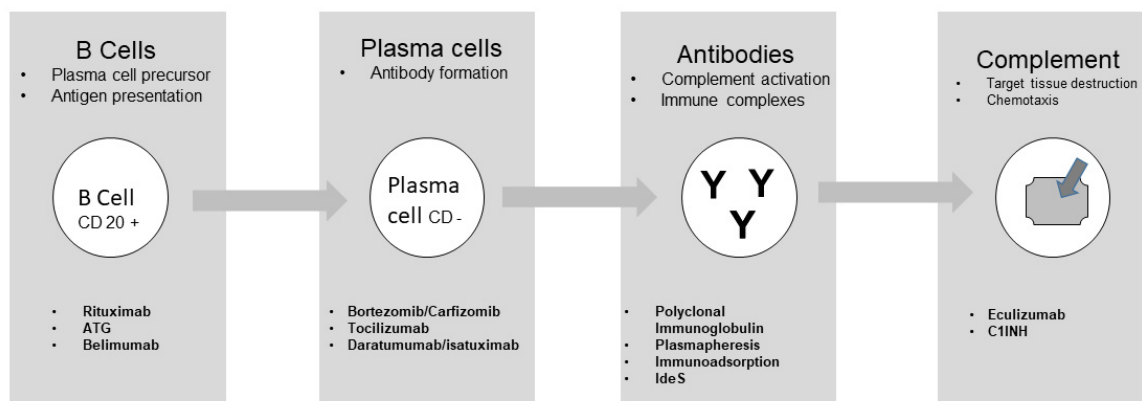
In the case of living donation, an early pre-transplant desensitization is preferred until obtaining CDC or Flow X-match-negative. Clearly different drugs at different dosages may be applied. In case deceased donors do not exist for enough time, two strategies may essentially be applied: the immediate pre-transplant desensitization as used principally in Austria [23] or the post-transplant desensitization as used at the Necker Hospital in Paris [24].

In the case of immediate pre-transplant desensitization, Immunoabsorption (IA) is the preferred method due to its ability to efficiently remove IgG [25,26]. The IA treatment is immediately followed by the administration of anti-thymoglobulin (ATG) and/or anti-CD20 (rituximab). The graft survival rates at 3 years are similar in CDCXM-positive and in CDCXM-negative patients.

The protocol used at the Necker Hospital in the case of deceased donors consists of an induction therapy with ATG, which is started on the day of transplantation, followed by high-dose immunoglobulin (IVIg) that is repeated every 3 weeks for a total of four courses. At the end of plasmapheresis, 1 or 2 rituximab infusions are administered. The graft survival rates 7 years post transplantation are 80% even if lower than the graft survival of the control group represented by patients that do not need desensitization.

### 6. Desensitization Strategies and Drugs

Summarizing what has been described above, four steps can be seen in the process leading to target tissue destruction. B cells are formed after antigen binding and B cells may act as antigen presentation and are precursors of plasma cells. The second step is represented by plasma cell formation with consequent antibody formation. The antibodies that form immune complexes and activate the complement represent the third step. Finally, complement activation induces chemotaxis and leads to target tissue destruction (Figure 1) [27].



**Figure 1.** Targeting different cells or functions.

Different drugs may act on each step described. These drugs are well described by the study of Jordan et al. [28] and their action is summarized in Table 2. In addition to the drugs described, there is an old but efficient pleiotropic drug that may act at any stage. This drug is intravenous immunoglobulin (IVIg), generally given at a dose of 2 g/kg multiple times. The efficacy of IVIg, frequently associated with other drugs, has already been described [24]. Vo et al. [29] conducted an interesting study documenting the efficacy of IVIg in association with rituximab in inducing desensitization.

**Table 2.** Summary of pharmacologic options.

Drug	Mechanism of Action
Rituximab	Murine/human mAb binding CD20 present on pre-B and mature lymphocytes
Daratumumab	IgG1k-humanized mAb directed against CD38
Eculizumab	mAb-binding protein C5, inhibiting cleavage to C5a and C5b and formation of membrane attack complex C5b-9
C1 esterase inhibitor	Inhibits activation of complement and intrinsic coagulation pathway
Tocilizumab	Recombinant humanized antihuman IL6 receptor mAb. Binds both soluble and membrane-bound IL6R
Clazakizumab	Genetically engineered, humanized IgG1 mAb; IL6 ligand inhibition
IgG-degrading enzyme of <i>S. pyogenes</i> . IdeS	Enzyme that cleaves all 4 IgG antibodies into F(ab)2 and Fc

## 7. Drugs Acting on B Cells

Three main drugs act on B cells leading to their reduction and reducing their activity of Rituximab (RTX), ATG, and Belimumab. In a study of Ramos et al. [30] conducted on 25 recipients of living donors needing desensitization, the effectiveness of RTX, IVIg, and ATG in reducing the number of splenic B cells and plasma cells was evaluated. The effect of multiple plasmapheresis plus low-dose IVIg reduced naïve B cells, plasma cells, and memory B cells. Adding RTX to the treatment was effective in a further reduction in naïve B cells, without an effect on memory B cells and plasma cells. Finally, adding ATG to the treatment led to a reduction in memory B cells (CD27<sup>+</sup>), but again without any effect on plasma cells.

Belimumab inhibits the growth and differentiation of B cells by blocking B lymphocyte stimulator (BAFF or BlyS). Indeed, in normal conditions, BAFF binds to the receptors, BAFF-R, B cell maturation antigen (BCMA), and transmembrane activator and CAML interactor (TACI), leading to immature B cell survival and maturation, plasma cell survival, and B cell survival and proliferation [31–33]. Belimumab is a complete human IgG1 $\lambda$  recombinant monoclonal antibody directed against BAFF, initially used for the treatment of systemic lupus erythematosus (SLE) [34].

Belimumab monotherapy was studied as a desensitization agent in kidney transplantation. Nevertheless, the study was terminated early for a reported lack of efficacy (NCT01025193) [35].

Another phase 2 double-blinded randomized placebo-controlled trial of Belimumab plus standard-of-care therapy is being examined for prevention of allograft rejection in renal transplant recipients (NCT01536379) [36]. Finally, the study of Banham et al. [37] in an experimental medicine, randomized, placebo-controlled trial documented the efficacy of Belimumab. In this study, the concentration of activated memory B cells decreased from week 21 to 28 of the treatment and the addition of Belimumab to standard-of-care immunosuppression significantly reduced de novo IgG antibodies.

## 8. Drugs Acting on Plasma Cells

The second step is represented by plasma cells both short and long living that are principally responsible for antibody production. Fc $\gamma$ RIIb, which is an inhibitory receptor for the Fc portion of IgG, controls the persistence and apoptosis of bone marrow plasma cells. It is expressed on B cells [38]. The crosslinking of Fc $\gamma$ RIIb on naïve B cells may induce apoptosis of B cells [39,40]. Another study documented that Fc $\gamma$ RIIb controls bone marrow plasma cells and, when crosslinked, induces plasma cells apoptosis [41]. Inside the germinal centers, the balance between survival and apoptosis is related to several factors, such as Fc $\gamma$ RIIB. Indeed, the overexpression of Fc $\gamma$ RIIB regulates protein phosphorylation and suppresses B cell activation to ameliorate SLE, as documented in mice and in vitro. [42].

A drug efficient in acting against plasma cells is proteasome inhibitors. It is well documented that after proteasome inhibitor administration such as Bortezomib, there is a reduction in the number of antigen-specific plasma cells in candidates of living-donor kidney transplantation [43]. Bortezomib is able to reduce serum levels of DSAs in patients, which were not affected by IVIg or RTX. In addition, Bortezomib reduces the number of antigen-specific plasma cells, without decreasing the total number of plasma cells. In a different study [44], proteasome inhibition caused apoptosis of normal human plasma cells, preventing alloantibody production. Treatment with Bortezomib resulted in a significant increase in the percentage of apoptotic cells, while RTX, ATG, and IVIg had no effect.

However, in different well-conducted studies, Bortezomib did not confirm its efficacy compared to other treatments in reducing DSAs after transplantation in sensitized patients. In particular, Ejaz et al. [45] divided their patients into four groups. One group received ATG alone, a second group received ATG + RTX, a third group received ATG + Bortezomib, and a fourth group received ATG + RTX + Bortezomib. The results in their capacity to reduce DSAs post transplant were similar for all groups, as shown in Table 3. Similarly, Eskandary et al. [46] conducted the study BORTEJECT. The study was a randomized,

placebo-controlled trial to investigate the effect of Bortezomib on the course of late ABMR. Bortezomib given as a single agent did not obtain an improvement in the course of late rejection. These studies called for new, more effective agents acting on plasma cells. Carfilzomib is a second-generation irreversible proteasome inhibitor. It is an epoxyketone nonboronated molecule that proved to be effective and with a reduced toxicity in the treatment of patients with multiple myeloma [47]. In a randomized clinical trial (NCT02442648) [48], the B-cell-targeted desensitization with Carfilzomib for preformed anti-HLA antibodies in patients awaiting kidney transplantation was evaluated. A study from Tremblay et al. evaluated the prospective [49], iterative, adaptive trial of carfilzomib-based desensitization. The study documented that HLA antibodies were substantially reduced in the group treated with carfilzomib alone.

**Table 3.** DSA monitoring for the first year after transplantation with different treatments [45].

	rATG Alone (n = 10)	rATG + RTX (n = 10)	rATG + Bortezomib (n = 10)	rATG + RTX + Bortezomib (n = 10)	p-Value
Development of de novo DSA	3/10 (30%)	3/10 (30%)	1/10 (10%)	3/10 (30%)	0.70
Time to de novo iDSA appearance (days)	38	101	10	185	0.33
Time to de novo iDSA peak (days)	38	323	11	186	0.13
De novo iDSA level at the end of 1-year follow-up (MFI)	0	0	0	0	0.68
Number of patients with increase in de novo iDSA	0/3	1/3	0/1	0/3	1.00
Number of patients with decrease in de novo iDSA	3/3	2/3	1/1	3/3	1.00

A different strategy for effective desensitization is the use of the Interleukin-6-receptor-specific humanized monoclonal antibody, better known as Tocilizumab. Indeed, IL-6 promotes B cell differentiation to plasma cells and induces Th17 cells. Vo et al. [50] used Tocilizumab in addition to IVIg in patients difficult to desensitize. In their study, Tocilizumab reduced DSA strength and numbers at transplant and 12 months after transplantation. Protocol biopsies showed no evidence of antibody-mediated rejection or transplant glomerulopathy. In the study, after effective desensitization and transplantation, patients subsequently received IVIg once and Tocilizumab monthly for 6 months. The number of patients is low and the authors themselves highlight that larger controlled studies are needed. Later on, Doberer et al. [51] verified the efficacy of a different anti-IL-6 antibody, Clazakizumab, on late ABMR. Clazakizumab is a humanized monoclonal IgG1 antibody. Compared to Tocilizumab, it has a higher affinity for IL-6 and a longer half-life, as documented by studies on psoriatic arthritis [52].

The receptor specific for plasma cells is CD38. Daratumumab is a human immunoglobulin IgGk1 monoclonal antibody that targets the CD38 surface antigen on plasma cells. Daratumumab has been used successfully in treating multiple myeloma and AL amyloidosis. Moreover, unlike Bortezomib, Daratumumab targets nonmalignant plasma cells, hence its efficacy in desensitization and in treatment of ABMR [53,54].

Daratumumab has been successfully used in sensitized kidney transplantation in a nonhuman primate model [55]. Recently [56], four cases of transplant patients desensitized and treated with Daratumumab for AMBR have been reported [55,57–59] (Table 4).

**Table 4.** Results of 4 patients with ABMR treated by anti CD38 [56].

Transplant	Sensitization	Treatment	Anticd38 Use	Evolution
Heart + kidney	Immunized: Preformed DSA	Steroid Pulse +ATG+IVIg+RTX+ Eculizumab	16 mg/kg infusion for 8 weeks	Clinical good HLA dramatic decline
Kidney	Immunized: preformed DSA	No treatment added to the standard of care	16 mg/kg for 8 weeks + 1 monthly infusion for 9 months	DSA undetectable Stabilization of renal function
Kidney	Immunized: AB0i (Anti A)	Steroid pulses ATG Immunoadsorption Eculizumab	16 mg/kg for 6-week infusions	Kidney function recovered Reduction in anti A titer
Heart	Immunized: Preformed DSA	Steroid pulses Immunoadsorption	16 mg/kg infusion for 8 weeks + 1 infusion monthly for 9 months	Improvement Only slight reduction in DSA

Another drug acting on DSAs is Belatacept, but its efficacy is only documented when associated with proteasome inhibitors as documented by the studies of Alishetti et al. and of Jain et al. [60,61].

A clinical trial is ongoing (NCT04827979) [62] to verify the efficacy of Belatacept when associated with Daratumumab.

## 9. Drugs Acting on Antibodies

Plasma cells produce antibodies that are dangerous by generating immune complexes and by activating the complement cascade.

Removal of DSA antibodies is essential in the different methods of desensitization or in the treatment of ABMR.

The use of IVIg has already been described and represents an important strategy for desensitization as used at the Necker Hospital [24].

A pioneer study suggested that polyclonal Ig could be efficient in decreasing anti-HLA antibodies [63]. Later on, a randomized trial (NIH IG02) compared the pre-transplant administration of polyclonal Ig with placebo in highly sensitized patients [64]. Unfortunately, the NIH IG02 documented that, even if the transplantation rates were higher in the IVIg group, there was only a mild and transient effect on PRA. This fact led to a higher incidence of ABMR in the IVIg treatment group.

IVIg seems to be more efficient when associated with mechanical antibody removal as obtained with plasmapheresis. Montgomery et al. [65] conducted a study in sensitized living-donor kidney transplant recipients. Desensitization was conducted with a combination of plasmapheresis (PE) and administration of IVIg. Post-transplant ABMR occurred as an effect of antibody rebound after contact with allogenic antigens. The ABMRs were easier to control with new cycles of PE and low-dose IVIg. As recommended by the already mentioned desensitization protocol [24], it is essential that the administration of IVIg always follows the PE to avoid the removal of Ig with the PE treatment.

According to the European Guideline for the management of kidney transplant patients with HLA antibodies, both PE and Immunoadsorption are effective [66]. Their efficacy is higher when associated with IVIg and RTX. IA is more selective and is the preferred method by some authors, particularly in the preparation of AB0-incompatible kidney transplantation [67–69].

A different method to neutralize antibodies is the use of the IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS) that cleaves intact IgG. Intact human IgG is cleaved by IdeS in two steps. The first step results in a single cleavage of the IgG molecule in which one heavy chain remains intact. The second step generates a fully cleaved molecule that cannot mediate complement-dependent cytotoxicity (CDC) or antibody-dependent cytotoxicity (ADCC) by means of Fcγ receptors [70,71]. A study from Jordan et al. [72]

represents the first pilot study that combines two phase 1–2 trials undertaken independently. Overall, 25 highly immunized recipients were treated: 14 in the USA and 11 in Sweden. One shot of IdeS 4 to 6 h was taken before transplantation. IdeS is extremely potent at cleaving circulating IgG, but the effect may be transient. The extent and frequency of DSA rebound after transplantation highly varied between the Swedish and the American arms of the study. Indeed, in the Swedish group, DSAs remained undetectable up to 14 days from transplantation, with a subsequent rebound. In the USA patients, the rebound was very low. This is possibly the effect of the use of IVIg plus RTX before and after transplantation [73,74].

Later on, the safety and efficacy of IdeS were documented by the studies of Lorant [75] and Ge et al. [76].

## 10. Drugs Acting on Complement

The fourth and final step to be targeted is the complement that favors chemotaxis and leads to tissue destruction. It has been documented that terminal complement inhibition decreases ABMR rates in sensitized renal transplant recipients [77]. In this study, complement inhibition and desensitization were obtained with the use of the anti C5 eculizumab. Eculizumab was given at a dose of 1200 mg immediately prior to transplantation, 600 mg on postoperative day 1, and 600 mg weekly for 4 weeks. Eculizumab was then discontinued if DSAs had significantly decreased or continued until the B flow crossmatch channel shift was <200. Graft survival and ABMR rates were significantly lower in the eculizumab group than the control group. However, considering the outcomes beyond 1 year, the incidence of transplant glomerulopathy did not differ in the two groups [78]. In a more recent study, Marks et al. [79] conducted a randomized trial on the safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization. There were lower rates of ABMR in the eculizumab arm than the arm with standard-of-care therapy. However, at 3 years, there were similar graft survival rates.

A different and new way of targeting the complement is to target the enzymes of the initiating complement cascade [80]. This can be obtained by the use of the serine protease inhibitor (C1INH) [81]. There are two forms of C1INH: the ultra-pure derived C1INH and the full-length recombinant C1INH. These drugs have their advantages and their drawbacks. An advantage is represented by the knowledge of the drugs because they represent the standard of care for hereditary angioedema [82,83]. Additionally, plasma-derived molecules are not immunogenic and they have a broad effect on classical and lectin pathways. The main drawback is the lack of specificity. Indeed, C1INH also controls mannose-binding lectin-associated serine protease (MASP) and proteases in the coagulation and kinin systems. These drugs are new and promising. Indeed, Vo et al. reported that C1-INH resulted in significant elevations in C1-INH levels, C3, and C4, and reduced C1q+HLA antibodies, and that the combination of antibody reduction and C1-INH may prove useful in the prevention and treatment of AMR. Anyway, further controlled studies are warranted [84].

## 11. Conclusions

The improvement of techniques to detect both serological and cellular memory in recipients waiting for kidney transplantation has allowed us to detect a larger number of sensitized patients than previously achieved. As a consequence, the improvement of drugs and strategies to allow desensitization is of utmost importance. In particular, new drugs acting on plasma cells, on antibodies and on complement cascades are promising.

## 12. Future Directions

New drugs acting on different cells and proteins involved in sensitization and acting on ABMR represent the most important developments for the future. Many trials are ongoing to verify the efficacy and safety of proteasome second-generation and new anti



IL-6 monoclonal antibodies. Similarly, new complement inhibitors have been reported as highly promising. Finally, the association of two or more desensitizing drugs, such as belatacept in association with daratumumab, is an interesting avenue to explore.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed consent Statement:** Not applicable.

**Data availability Statement:** Not applicable.

**Conflicts of Interest:** The author declare no conflict of interest.

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