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RISKS AND WAYS OF PREVENTING KIDNEY DYSFUNCTION IN DRUG-INDUCED IMMUNOSUPPRESSION IN SOLID ORGAN RECIPIENTS

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Immunosuppressive therapy (IMT) is the cornerstone of treatment after transplantation. The goal of immunosuppression is to prevent acute and chronic rejection while maximizing patient survival and long-term graft function. However, the expected effects of IMT must be balanced against the major adverse effects of these drugs and their toxicity. The purpose of this review is to summarize world experience on current immunosuppressive strategies and to assess their effects on renal function.

Keywords: organ transplantation, induction therapy, immunosuppressive therapy, adverse events, renal failure.

INTRODUCTION

Organ transplantation is the method of choice in the treatment of patients with irreversible loss of vital organ function. Achieving the desired results is possible with optimal use and a deep understanding of IMT that is aimed at preventing acute and chronic allograft rejection. The beginning of widespread use of calcineurin inhibitors (CNIs) was an important milestone in the evolution of IMT, significantly reducing the incidence of acute rejection [1]. This review discusses advances and techniques in IMT that have emerged over the past 50 years in the practice of clinical transplantology. The possibilities and limitations of these advances and how they affect current outcomes in post-transplant patients are also assessed.

I. IMMUNOSUPPRESSANTS AND RENAL FUNCTION IN EXTRARENAL ORGAN TRANSPLANTATION

Prolonged survival of donor organ recipients has led to greater exposure to immunosuppressants and increased adverse events associated with their use. Today, the main causes of late post-transplant mortality are largely due to long-term use of immunosuppressants [2]. Since the beginning of the decade, more than two-thirds of post-liver transplant deaths are unrelated to liver graft function, which underlines the effectiveness of modern IMT regimens [3]. However, the good survival rate of liver recipients has demonstrated the role of adverse events associated with prolonged exposure to IMT on the recipient's body. With better survival rates in solid organ recipients, reports on the detection of chronic kidney disease (CKD) in child recipients of extrarenal transplants began to appear [4, 5]. The incidence of CKD in pediatric donor heart, lung, and liver recipients ranges from 8% to 38%, depending on the definition and duration of post-transplant follow-up [4–6].

Ruebner et al analyzed data from over 16,000 children who underwent extrarenal organ transplantation between 1990 and 2010. During a median follow-up of 6.2 years, end-stage renal disease (ESRD) developed in 3% (n = 426) [4]. Choudhry et al also studied the Scientific Registry of Transplant Recipients (SRTR) and the United States Renal Data System (USRDS) databases and found that during a median follow-up of 11.8 years, ESRD developed in 4% of heart recipients [7]. The actuarial risk of developing ESRD after heart transplantation was 3% at 10 years and 16% at 20 years.

In a retrospective cohort study, Menon et al. assessed the risk of acute kidney injury (AKI) and CKD in solid organ recipients. The study included patients under 21 years of age who underwent liver (n = 112) or heart transplantation (n = 109) between July 1, 2009, and December 31, 2016. Pediatric AKI was seen in 63% (n = 69) after heart and 43% (n = 43) after liver transplant. Cumulative incidence (95% CI) of CKD stages 3–5 at 60 months post-heart transplant was 40.9% (27.9–57.1%) in patients with AKI vs 35.8% (17.1–64.8%) in those without (P = NS). Post-liver transplant, the cumulative incidence of CKD stages 3–5 at 60 months was 0% in those without perioperative AKI vs 10% (3.2–29.3%) in those with (P = 0.01). Patients with perioperative AKI

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had lower estimated glomerular filtration (eGFR) at last follow-up [8].

Kidneys in recipients of extrarenal organs often begin to suffer at the pre-transplant stage. The use of calcineurin inhibitors (as a component of maintenance immunosuppression) and baseline renal dysfunction are traditionally considered risk factors for CKD [4, 5, 7]. Other provoking factors are infection, arterial hypertension and other nephrotoxic drugs [5, 8]. Kidney injury is a common event after extrarenal organ transplantation in adults [10–12]. Studies show that in adults after extrarenal organ transplantation, the decline in renal function is most pronounced in the first six months after transplantation, and renal dysfunction progresses more slowly or even stabilizes thereafter [13]. Even a single episode of AKI developing in the first three months after transplantation is associated with a threefold increased risk of CKD [5]. Renal failure persisting one month after liver transplantation is associated with increased risk of CKD [14]. CKD and ESRD are reported in 70% and 8.5% of patients, respectively, in the long term after liver transplantation [15]. Although kidney injury in non-renal transplant recipients is caused by multifactorial mechanisms, calcineurin inhibitor-induced renal arteriole vasoconstriction plays a leading role [16, 17]. Due to the high significance of kidney injury in clinical practice, a nephroprotection strategy is being developed, which is conventionally divided into early and late.

Early nephroprotection strategy includes induction immunosuppression with delayed administration of low-dose CNIs in combination with non-nephrotoxic immunosuppressants to safely minimize CNIs.

Induction IMT in liver transplantation is used less frequently than in other organ transplantation because of the lower risk of rejection and the often-severe clinical condition of patients with cirrhosis at the time of transplantation. In the United States, only 20–25% of liver recipients receive induction immunosuppression. Nevertheless, induction with rabbit antithymocyte globulin (rATG) appears to be reasonable in liver recipients with impaired renal function [18].

A United Network for Organ Sharing registry study [19] showed that lymphocyte-depleting agents like alemtuzumab and rATG, especially in combination with steroids, appear to be more effective in preventing renal dysfunction than agents that do not affect on liver recipients' lymphocyte counts (basiliximab and daclizumab).

Because of the existing data on the correlation between CNI levels, early renal dysfunction, and mortality, many induction immunosuppression protocols have been studied as part of a strategy to minimize CNIs in order to preserve renal function. The use of anti-CD-25 monoclonal antibodies for induction allows minimal starting doses of CNIs to be administered or delayed in liver recipients with acute kidney injury. This approach leads to a more rapid recovery of renal function with a comparable or even lower rejection rate [20]. In a more recent study by Pratima Sharma et al, the results were not as clear-cut. In a group of liver recipients with severe renal dysfunction, delayed tacrolimus (TAC) initiation combined with basiliximab induction therapy had no durable effect on long-term post-transplant outcome [21].

Standard residual tacrolimus trough levels (TAC C0) in randomized controlled trials ranged from 10 to 15 ng/mL. Combination with mycophenolate mofetil (MMF) can safely reduce TAC C0 levels to 7–10 ng/ml, with a similar incidence of acute rejection with better renal function, metabolic and cardiovascular profile [22]. The possibility of using mammalian target of rapamycin (mTOR) inhibitors, at one time caused considerable interest, due to the better safety profile in terms of renal function and high immunosuppressive efficacy. Unfortunately, the combination of TAC with rapamycin (RAP) in de novo transplanted patients showed an increased risk of hepatic artery thrombosis and acute graft rejection compared to the group on the standard IMT regimen, which required early termination of the study [23]. In another study comparing the combination of RAP with MMF versus TAC with MMF, there was a significant improvement in renal function four weeks after liver transplantation, but an increased rate of rejection in the RAP group [24]. A randomized controlled trial H2304 compared a combination of everolimus (EVE) with low-dose TAC, EVE without TAC, and a conventional TAC regimen. At month 12, 24 and 36, renal function was better in the EVE group with low-dose TAC, and the study in the EVE group without TAC was terminated early because of the high rate of acute rejection there [25].

Similar results were obtained in the PROTECT study, which compared the combination of EVE with a reduction in CNIs 8–16 weeks after liver transplantation with standard CNI doses. Better kidney function in the group of patients receiving EVE was observed for 5 years [26]. One meta-analysis of randomized controlled trials of adult recipients after de novo liver transplantation who received EVE in combination with low-dose TAC, or without TAC, found that they were associated with improved renal function at 12 months with similar efficacy in terms of rejection or mortality [27]. A number of centers have suggested the use of a combination of mTOR inhibitors with low-dose TAC starting in the immediate postoperative period. Unfortunately, there is no convincing evidence to support the effectiveness of this strategy [28]. It should be noted that IMT regimens without CNIs have also been proposed as options for therapy after induction immunosuppression with a combination of monoclonal and polyclonal antibodies. A high rejection rate has been reported for this protocol [29]. An attempt to replace nephrotoxic CNIs with belatacept (BEL), a costimulation blocker, showed an improvement in renal function one year after transplan-

tation. However, the study was prematurely terminated due to an unexplained increase in deaths in the group of patients receiving BEL [30].

Nephroprotection strategy in the late post-transplant period

Late conversion, 1 year or more after transplantation, from CNIs to RAP, showed no significant effect on renal function, with a high rate of rejection and side effects of RAP necessitating a return to CNIs [31]. Two large, but relatively old, randomized controlled trials of conversion from CNIs to a combination of EVE with low-dose TAC at one to five years showed a comparable probability of developing acute rejection with no significant effect on renal function [32, 33].

Another retrospective study examined the efficacy of conversion to EVE, in patients with impaired renal function following liver transplantation. Improvement in renal function at 12 months was achieved in the group of patients in whom conversion was performed no later than 1 year after liver transplantation [34]. The strategy of conversion to MMF monotherapy or their combination with low-dose CNIs resulted in better renal function if performed no later than 2 years after transplantation. A systematic review that summarized the switch to MMF concluded that it demonstrated beneficial effects on renal function, with an increased risk of developing rejection [35]. On the other hand, there is evidence that even with complete withdrawal of immunosuppression in liver recipients, which has been achieved in some cases [36, 37, 38], no studies have reported beneficial effects of such withdrawal in terms of renal function, hypertension, diabetes or hyperlipidemia [2].

II. MAJOR IMMUNOSUPPRESSANTS

A. Glucocorticoids (GCs)

Glucocorticoids (GCs) were used as first-line drugs in organ transplantation even before the advent of azathioprine (AZA) and cyclosporine (CsA). They were used as immunosuppressive agents as well as maintenance therapy to prevent acute rejection. GCs are anti-inflammatory agents, and their immunosuppressive effect results from several mechanisms. They act through glucocorticoid receptor (GCR) [39]. The genomic effects of GCs are realized within a few hours of drug administration [40]. GCs also produce immediate effects occurring within seconds or minutes and are referred to as nongenomic glucocorticoid effect [41]. Collectively, GCs disrupt or inhibit various cellular activities such as migration, phagocytosis, and release of inflammatory chemokines and cytokines from various cells. GCs also accelerate lymphocyte apoptosis and interrupt immune responses to foreign antigens. Clinically, these effects of GCs are associated with increased risk of bacterial, viral and fungal infections in the recipient. GCs are an integral component of induction IMT, but their use as a component of maintenance IMT is not as straightforward. Adverse effects of GCs include mineral-bone disorders, infectious complications [42], cataracts, hyperlipidemia, aseptic necrosis of the femoral head, osteoporosis, mood changes and a Cushingoid appearance; long-term use of GCs in children leads to growth retardation [43]. The frequency of arterial hypertension associated with the use of GCs is about 15%, and in almost 10% of cases, GCs are the cause of impaired glucose tolerance i.e., the so-called post-transplant diabetes mellitus (PTDM) [44]. Hence, minimizing the use of GCs may improve graft and patient survival [45].

A meta-analysis of seven studies evaluating the effects of CsA-based, steroid-free IMT protocols on graft and patient survival and incidence of acute graft rejection demonstrated that absence or withdrawal of GCs increased the risks of acute rejection but had no adverse effect on patient or graft survival. Since only one study evaluated patient and graft survival two years after transplantation, no reliable long-term conclusions on the risk of chronic rejection or graft loss could be drawn [46]. A meta-analysis of ten other studies demonstrated an increased risk of acute cellular rejection (ACR) in groups of patients in whom GCs were abolished, along with increased relative risk of graft dysfunction [47]. Because of the inconsistency of the findings and the use of AZA as a component of maintenance IMT in these studies, a third meta-analysis included only randomized controlled trials of patients receiving CNIs and MMF. This study concluded that late withdrawal of GCs was associated with a higher incidence of ACR but had no adverse effect on graft survival in the medium term [48]. Since most transplant centers today use induction IMT followed by TAC and MMF maintenance therapy, many protocols provide for either rapid withdrawal of GCs or complete rejection of their use [49].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state that in patients who are at low immunological risk and who receive induction IMT with lymphocyte-depleting antibodies, GCs can be discontinued within the first week of transplantation [47, 50]. These recommendations are supported by a meta-analysis of 9 studies, in 5 of which maintenance IMT was based on TAC administration, and in 4 – on CsA, in one study mTOR inhibitor was used [51]. Mortality and graft loss were similar in both patients receiving GCs and patients on steroid-free protocols [52]. These data are consistent with the observation from an analysis of US registry data showing that de novo immunosuppression without GCs did not increase the risk of adverse clinical outcomes in the medium term [53].

B. Antiproliferative drugs: azathioprine and mycophenolate mofetil

1. Azathioprine

AZA belongs to the class of antimetabolites, an imidazoline derivative of 6-mercaptopurine. AZA is a structural equivalent of adenine, hypoxanthine and guanine, which are part of nucleic acids [54]. Inhibition of purine synthesis de novo blocks lymphocyte proliferation [55]. 6-mercaptopurine is metabolized to 6-thioguanosine-5'-monophosphate, which is further metabolized by a series of kinases and reductases to form deoxy-6-thioguanosine-5'-triphosphate. Cell cycle arrest and apoptosis are triggered by incorporation of deoxy-6-thioguanosine-5'-triphosphate into the cell DNA [56]. AZA was found to block the CD28 costimulation pathway, thereby inhibiting the proliferation of activated lymphocytes [57]. AZA, along with GCs and CsA, was the immunosuppressant of choice after organ transplantation, until several randomized trials comparing it to MMF demonstrated significant advantages of the latter. [58].

2. Mycophenolate mofetil

MMF is the 2-morpholinoethyl ester of mycophenolic acid (MFA). MMF is a potent selective noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, which inhibits de novo synthesis of guanosine nucleotides in T and B cells [59, 60]. Moreover, MMF predominantly inhibits inosine monophosphate dehydrogenase 2, whose activity is increased in activated lymphocytes, and, consequently, MMF has the greatest effect on proliferation of activated lymphocytes and reduces cytokine and antibody production induced by allergens and mitogens [61]. This selective effect is a factor that provides a better safety profile of MMF compared to azathiprine or cyclophosphamide [62]. In addition to the antiproliferative effect on lymphocytes, MPA has other mechanisms of action: due to depletion of guanosine triphosphate reserves, fucosylation and surface expression of lymphocyte and monocyte adhesion molecules are impaired [63]. MMF inhibits the surface expression of antigens responsible for differentiation and efficient presentation of allergens by dendritic cells, thus suppressing adaptive immune response [64]. Another advantage of MPA is its nephroprotective effect observed in patients with chronic graft nephropathy [65]. A review of 19 studies comparing the effectiveness of MMF and AZA in combination with CNIs demonstrated that the use of MMF provides a positive clinical effect by reducing the absolute risk of acute rejection or graft loss [66].

C. Calcineurin inhibitors

Introduction of CNIs into clinical practice has resulted in increased graft survival without rejection. However, the use of CsA or TAC requires frequent monitoring of blood levels because of their very narrow therapeutic index. Narrow therapeutic index, high individual variability, and poorly predictable and variable oral bioavailability put these drugs at risk for serious adverse effects [67]. The best-known side effect is nephrotoxicity, which has been detected almost since the beginning of clinical use [68]. Another undesirable effect of CNIs is the development of insulin resistance. Although TAC is considered less nephrotoxic than CsA, it is up to 5 times more diabetogenic, which provokes the development of PTDM. In the long term, PTDM is associated with impaired renal function and worsened patient survival [69]. Another problem with the use of CNIs is neurotoxicity, which can occur at both therapeutic and toxic levels of the drug. The main manifestation of neurotoxicity is the posterior reversible encephalopathy syndrome, whose radiological sign is a change in signal intensity reflecting vasogenic cerebral edema, localized mainly in the posterior parieto-occipital regions of the brain [70]. Today, TAC is considered to be the preferred CNI in all types of solid organ transplantation because of its ability to better control the risks of acute rejection reaction and potentially less nephrotoxicity [67].

The Efficacy Limiting Toxicity Elimination (ELITE)–Symphony study compared four groups of patients after kidney transplantation: group 1, those who received standard-dose CsA with a minimum concentration (C0) of 200–300 ng/mL; group 2, those who received low-dose CsA with C0 equal to 100–200 ng/mL; group 3, those who received low-dose TAC with C0 equal to 4–7 ng/mL; group 4, those who received low-dose sirolimus (SRL) with C0 4–8 ng/mL. All patients received induction IMT with daclizumab and received MMF and GCs as maintenance therapy. Incidence of acute rejection was lower in group 3 patients. Allograft survival differed significantly among the four groups and was highest in the low-dose TAC group. At the same time, serious adverse events were more common in the low-dose SRL group [71]. These trends were observed over a 3-year period [72]. This study provided reliable evidence of the effectiveness of maintenance IMT based on a TAC + MMF + and + GCs combination for renal transplant recipients.

D. Mammalian target of rapamycin inhibitors: Sirolimus and Everolimus

SRL or RAP, a secondary metabolite produced by S. hygroscopicus, was obtained in the 1970s [73]. EVE is a derivative of RAP, characterized by increased bioavailability when ingested and a shorter half-life [74]. mTor inhibitors significantly inhibit IL-2-stimulated T-cell proliferation and also affect B cells by inhibiting their antigen- and cytokine-dependent proliferation [75]. RAP has been shown to inhibit cytokine-dependent (IL-2, IL-6) differentiation of B cells into plasma cells, thus suppressing immunoglobulin synthesis [76]. The side

effects of mTOR inhibitors include hyperlipidemia, thrombocytopenia, mucositis, edema, and proteinuria [77]. No nephrotoxicity has been found for mTOR inhibitors [78]. The premise of using mTOR inhibitors was to avoid adverse effects – chronic nephrotoxicity inherent to CNIs. A combination of RAP or EVE with a standard-dose CsA has been associated with increased risk of nephrotoxicity [79]. Therefore, attempts have been made to use RAP instead of CNIs. A study of a combination of RAP with MPA in renal transplant recipients demonstrated increased risk of rejection [80]. Subsequent studies have explored the potential of RAP, either as a salvage therapy to replace CNIs early after transplantation [81], or in patients with a "problematic" kidney transplant [82]. Also, mTOR inhibitors were studied as a means of preserving renal function in recipients of other organs with elevated creatinine levels on the background of CsA or TAC treatment [83–85].

The potential of EVE has inspired cautious hope in heart transplantation, and its combination with TAC appears to be a safe alternative to TAC- and MMF-based maintenance therapy [86]. In heart recipients without proteinuria, EVE can be used to minimize the CsA dose. Since up to 20% of liver transplant recipients develop end-stage CKD, administration of EVE in combination with low-dose CNIs has been studied in liver transplant recipients [87]. Data from a 3-year randomized trial demonstrate long-term preservation of kidney function in liver recipients with no loss of efficacy when CNIs are withdrawn early, and EVE continued [88]. The advantages of mTOR inhibitors also include their ability to block endothelial proliferation, the ability to suppress viral replication and some types of tumor cells. In this regard, RAP and EVE are used instead of CNIs for secondary prevention of neoplasia such as skin cancer, Kaposi's sarcoma and hepatocellular carcinoma, and post-transplant lymphoproliferative disorders [89].

E. Belatacept

BEL is based on abatacept (CTLA-4 Ig), a recombinant immunoglobulin that consists of the extracellular part of the CTLA-4 molecule and the constant IgG domain [90]. It is approved for prevention of graft rejection and it excludes CNI-related nephrotoxicity after kidney transplantation [91, 92]. Studies such as BENEFIT and BENEFIT-EXT have found that the use of BEL instead of CsA preserves kidney function [93]. There was increased ACR incidence in patients who received BEL compared to those who received CsA. However, this did not affect graft function at year 3 and 5 of follow-up. This is due to the fact that BEL is less effective than CsA in preventing early, but not late rejection [94]. In addition, only a small fraction of patients on BEL-based maintenance therapy form donor-specific antibodies (3% versus 8% on CsA). Besides, BEL-based maintenance therapy, compared with CsA, provides a better cardiovascular and metabolic risk profile, and is also associated with a lower risk of PTDM [95]. In a meta-analysis in which BEL was compared with CsA, an indirect assessment of the effectiveness of BEL, CsA, and TAC on graft and patient survival, acute rejection rates, and renal function was attempted [94, 96]. The study concluded that all three drugs provided comparable graft and patient survival. In addition, BEL was associated with significantly better GFR compared with CsA. Compared with TAC, this difference was clinically but not statistically significant. [97]. BEL is not used in transplantation of organs other than the kidney, except for a phase II study in liver transplantation that was terminated early due to increased risk of death and graft loss [30].

III. INDUCTION IMMUNOSUPPRESSIVE THERAPY

Based on the idea that during donor conditioning, organ removal, warm and cold ischemia, there is increased activation of immunogenic complexes, the concept of induction IMT began to be implemented. Another justification for the use of induction immunosuppression is the fact that the risk of acute rejection reactions is maximal in the first weeks and months after transplantation [98]. To date, two different categories of immunological agents used for induction IMT are available. The first includes lymphocyte-depleting antibodies: for example, polyclonal antibodies such as equine and rabbit antithymocyte immunoglobulin (rATG) [107], the second includes genetically engineered humanized IgG1 kappa monoclonal anti-CD52 antibodies [99]. As of 2008, 82% of kidney recipients received induction IMT drugs. In recipients of other organs, induction immunosuppression was used less frequently: 57% in lung transplantation, 47% in heart and 26% in liver transplantation. In transplantation of extrarenal organs, as a rule, non-lymphocyte depleting agents were used [100]. In 2020, immunosuppression induction was already used in 91% of kidney recipients, 1% less than in 2019. The main decrease in the use of lymphocyte-depleting agents occurred at the beginning of the COVID-19 pandemic [101].

A. Rabbit antithymocyte globulin (rATG, thymoglobulin)

rATG is a polyclonal antibody produced by rabbits after immunization with infantile human thymus tissue. rATG contains antibodies not only to T cells but also to many other antigens expressed in human thymus tissues [103]. It has been shown that rATG in vitro leads to an increase in regulatory CD4+CD25+FOXP3+ T cells that suppress the immune response to allergen and participate in tolerance induction [104, 105], and also suppresses genes involved in NF-κB regulation, costimulation, apoptosis, chemoattraction and dendritic cell function [106, 107]. A number of patients produce antibodies against

rabbit immunoglobulin. Antibodies are detected in more than 50% of patients after rATG administration, but their presence does not affect the efficacy of the drug [108]. Induction IMT with thymoglobulin compared to basiliximab in kidney recipients from a postmortem donor with a high risk of delayed function or acute rejection significantly reduced the probability of developing rejection, but did not affect the duration of graft dysfunction. Patient and graft survival were comparable in both groups [109].

B. Basiliximab (anti-CD-25 monoclonal antibody)

Basiliximab is a chimeric non-lymphocyte-destroying mouse/human monoclonal antibody targeted against the α-chain of IL-2R (also known as CD25 or IL-2Rα) [99, 110]. Acting as an IL-2Rα antagonist, basiliximab competitively inhibits lymphocyte activation. The main advantage when using anti-CD25 monoclonal antibodies is its specificity and the absence of leukopenia and thrombocytopenia, which are often observed when using lymphocytopenic antibodies.

Numerous randomized controlled trials have shown that basiliximab significantly reduces the risk of acute rejection compared with placebo in renal transplant recipients receiving double (CNIs and GCs) or triple IMT (CNIs, GCs and AZA or MMF). However, graft and patient survival rates at 12 months were comparable [111–113]. The effects of basiliximab appear to be even less pronounced when used as the main component of maintenance IMT using TAC. This may be due to the lack of large studies or to the more pronounced immunosuppressive effect of TAC compared to CsA [112]. At the same time, there is little information on the long-term effects of basiliximab. As for the safety profile of basiliximab, according to this study, it is an independent risk factor for PTDM [115].

C. Alemtuzumab (Campath-1H)

Alemtuzumab is a humanized rat monoclonal antibody originally designed to treat chronic lymphocytic leukemia (rat IgG2b); it is an antibody that targets the lymphocyte-specific surface marker CD52. The CD52 antigen is present on the surface of T cells, B cells, natural killer cells, macrophages, and monocytes [114, 116]. Even small doses of the drug cause persistent profound lymphopenia, and it may take considerable time to restore the number of lymphocytes. Alemtuzumab was first used for the purpose of induction IMT by Calne et al. in 1998 [117]. They suggested that the achieved profound depletion of lymphocyte level would minimize the dose of GCs, CNIs and even contribute to the development of immune system tolerance to the transplanted kidney. However, all patients developed reversible acute graft rejection within the first month [118]. Other studies have evaluated the efficacy and safety of alemtuzumab on maintenance therapy with CNIs or its combination with MMF [119]. In one study in patients at low immunological risk, biopsy-confirmed acute graft rejection within the first year was less common with alemtuzumab compared to standard induction IMT with basiliximab or rATG, while in high immunological risk the effectiveness of all three drugs was comparable [119]. Another review, which included 1,687 kidney transplants to adult recipients performed between January 1, 2002, and December 31, 2007, compared outcomes in patients who received alemtuzumab (n = 632), basiliximab (n = 690), or thymoglobulin (n = 125) as IMT inducers. Cumulative 1, 3, and 5-year survival rates were significantly lower in the alemtuzumab group, and the incidence of antibody-mediated rejection was higher. Alemtuzumab was found to be an independent risk factor for allograft loss ($P = 0.004$), opportunistic infections ($P = 0.01$), cytomegalovirus infections ($P = 0.001$) and antibody-mediated rejection ($P = 0.002$) [120]. An analysis of the elderly population showed that alemtuzumab appeared to be associated with increased risk of death and graft loss in this group [121]. A combination of induction alemtuzumab with RAP monotherapy was another attractive hypothesis and was tested on 29 patients. Eight patients required treatment for acute rejection and one patient had graft loss [122]. Other researchers have found that a combination of RAP with MMF after induction alemtuzumab was associated with a high rate of rejection and complications in the form of leukopenia and respiratory distress syndrome [123].

D. Other agents

Rituximab is an antitumor and immunomodulatory agent. It is a chimeric mouse/human monoclonal antibody that binds specifically to the CD20 transmembrane antigen [124]. Over the past 15 years, it has mainly been used in ABO-incompatible kidney transplants and has been used with varying degrees of success in protocols for desensitization of kidney transplant recipients and treatment of antibody-mediated rejection [125–127]. Data on the use of rituximab as an IMT inducer are still limited. Its efficacy has been evaluated in a prospective double-blind, randomized, placebo-controlled study [128]. The incidence of acute rejection as well as kidney function did not differ significantly between the rituximab group and placebo group. Another randomized controlled trial comparing rituximab with daclizumab was terminated early due to increased incidence of ACR in the rituximab group [129].

CONCLUSION

Since the mere fact of taking immunosuppressants has a negative effect, the goal of treatment is to prescribe the least immunosuppressive regimen that can reliably

prevent graft rejection. However, this simple concept presents many challenges when adapted to clinical practice. There are major differences in IMT regimens between different centers, between physicians at the same center, and even between physicians treating the same patient, but at different time periods. Moreover, reduction of immunosuppression regimen is based on surrogate markers (i.e., trough blood levels) and clinical events (i.e., rejection episodes, infectious complications). Because clinical practice lacks a reliable mechanism for assessing the adequacy of immunosuppression, it is very difficult to determine the minimum level of IMT that is sufficient for each individual patient at any given time. In addition, there are relatively few up-to-date studies describing IMT strategies in the available literature, and the average period of publications cited in current reviews dates back to 2011. All this determines the relevance of the search for new principles and modes of IMT, ensuring long-term survival of solid organ recipients, with minimal negative effects. The absence of new molecules preventing the development of rejection leaves clinicians with only the possibility to search for optimal combinations of existing immunosuppressants, used both at the induction stage and in further maintenance regimen.

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