TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

The need for minimization strategies: current problems of immunosuppression

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Keywords
immunosuppressants, kidney transplantation, long-term outcomes, minimization, side effects.

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Conflicts of interest
The authors have declared no conflicts of interest.

In honor of Prof H.H. Neumayer's retirement, who taught us drug minimization.

Received: 7 November 2014
Revision requested: 30 December 2014
Accepted: 27 February 2015
Published online: 18 March 2015

doi:10.1111/tri.12553

Summary

New immunosuppressants and the better use of immunosuppressant combination therapy have led to significant improvements in renal allograft outcomes over the last decades. Yet, despite dramatic reduction in rejection rates and improvement in 1-year graft survival, long-term graft attrition rates remained rather constant. Current immunosuppressant combinations are frequently leading to overimmunosuppression and are increasing cardiovascular risk. Importantly, calcineurin inhibitors are nephrotoxic, contribute to cardiovascular risk and chronic allograft dysfunction. Furthermore, immunosuppressant-associated toxicities aggravate immune-mediated nephron injury and side effects lead to nonadherence, an identified important reason for late acute and chronic antibody-mediated rejections. The frequent development of a chronic humoral response indicates rather insufficient immunosuppression of current combinations than simple under-immunosuppression. While there is no evidence that increasing immunosuppressive doses will improve outcomes or reduce de novo HLA-antibody formation, there is clear evidence that adequate minimization strategies will reduce side effect burden. Because of low rejection risk, but frequent side effects, drug minimization is particularly relevant for the many maintenance patients. In summary, new therapeutic strategies need to be developed from adequately powered clinical trials for reduction of the many side effects of immunosuppressants. Such evidence-based and time-dependent immunosuppressive minimization strategies are needed to achieve better long-term outcomes in the future.

Introduction

Current data [1] clearly demonstrate that renal transplantation improves survival of patients with end stage renal disease (ESRD). The quality of life and life expectancy of renal transplant recipients (RTR) dramatically improve, irrespective of age, gender, or cause of ESRD [1]. Today, excellent outcomes are achieved with more than 90% graft survival in the first year. The progress over the last two decades is largely due to the introduction and the better use of new immunosuppressants. Cyclosporine, the first calcineurin inhibitor (CNI), clearly revolutionized transplantation, allowing successful solid organ transplantation in the majority of patients. The introduction of tacrolimus, mycophenolate, mammalian target of rapamycin (mTor) inhibitors and Interleukin-2 receptor (IL-2R) antibodies led to further improvements and allowed multiple, highly effective combination therapies [2–4].

Yesterday, the main concern was to prevent acute rejection and to improve short-term graft and patient outcomes, because rejection rates were high while post-transplant expected survival was low. The addition of newer immunosuppressants dramatically improved efficacy and decreased the 1-year acute rejection incidence from 40–50% to 10–15% with an increase in 1-year graft survival from 80–85% to 90–95% [3]. Today, T-cell-mediated acute rejections are mostly reversible and, if treated successfully, have only a limited impact on long-term outcome. Late acute rejections

are rare, indicating very effective rejection prophylaxis with current drugs in the context of a lower immunological risk. Thus, current protocols are very efficient in preventing T-cell-mediated rejection, while less successful in preventing humoral B-cell-mediated immune responses. The incidence of antibody-mediated rejection (ABMR) with current protocols is difficult to quantify, depends on the immunological risk and time after transplantation, and is often associated with T-cell-mediated rejection [5]. A recent study, including 2316 RTR, showed an extremely low ABMR incidence of 1.3% (23/1839 patients) in the first year in compatible transplants, while 196/477 (41.1%) incompatible patients experienced ABMR [6]. In a longitudinal study, a total of 47/315 (15%) patients developed de novo DSA (dnDSA) at a mean of 4.6 ± 3.0 years post-transplant [7], but 18/47 (38%) patients with dnDSA had stable renal function during follow-up.

Today's immunosuppression after transplantation mainly relies on a multidrug combination therapy, each component with a different mechanism of action. Theoretically, we want to achieve an ideal therapeutic immunosuppression, which is just strong enough to prevent rejection, but does not lead to overimmunosuppression such as infection and cancer. Ideally, immunosuppressive drugs have synergistic efficacy leading to substantially lower dose requirements. The reduction of dose-dependent toxicities with relatively low dosing strategies in synergistic combinations resulted in better tolerability and efficacy. The Symphony trial [8,9] provide circumstantial evidence for the success of an early post-transplant minimization strategy. Together with mycophenolate and steroids, CNIs remain the cornerstone of initial immunosuppressive regimens due to a 1-year rejection risk reduction [3]. The combination of optimized immunosuppression with better diagnostics (e.g., HLA-antibody detection, CMV), better concomitant therapeutics (e.g., for CMV disease, for hypertension (e.g., renin–angiotensin blockers), better surgical standards, and many other factors (e.g., better detection and prevention of coagulation disorders) significantly decreased graft loss in the first year over the last 30 years. With such excellent short-term outcomes, it is difficult to demonstrate any improvements in efficacy, except for a reduction in side effects.

Decreasing time-dependent risk of rejection

Strong immunosuppression is particularly important during the initial post-transplant period (induction phase) when there is a high incidence of early post-transplant rejection. Most acute rejections occur in the first 6 months after transplantation, and current immunosuppressive protocols should aim to provide adequate immunosuppression early after transplantation. The transplant loss due to acute rejection is nowadays low, and the risk of rejection is markedly reduced after 6 months [10]. In later postoperative stages, "graft adaptation" occurs, resulting in the very low rejection rates in maintenance patients. The maintenance phase can be divided into early and late maintenance phase. Under standard therapy with tacrolimus and mycophenolate, the late maintenance phase (after the third year post-transplant) is characterized by an extremely low risk of acute rejection (<2%) [11]. Conversely, immunosuppressive toxicity remains frequent, partly due to increasing cumulative drug exposure over time.

As a consequence of the decreasing time-dependent immunological risk, immunosuppressants are reduced over time as reflected by only short induction, steroid tapering, and gradual lowering of CNI levels [12–14] (Fig. 1). While much evidence exists for the optimal immunosuppression in the first year, only sparse prospective data from a few large randomized trials provide some evidence for the maintenance period, which would be important for the majority of maintenance patients under long-term immunosuppression. Many centers continue triple maintenance therapy, others aim at twofold immunosuppressive strategies, and some low-risk patients are even maintained on

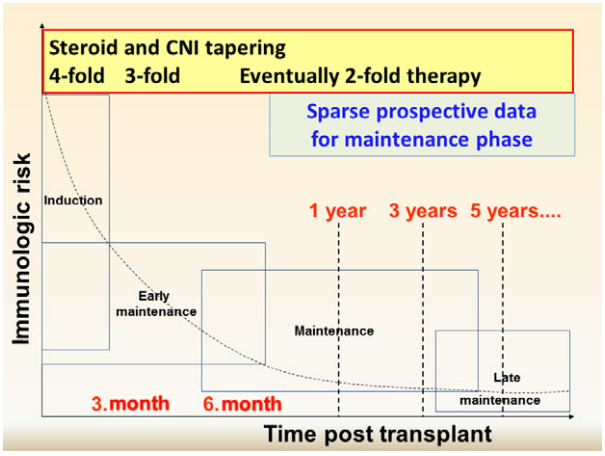

Figure 1 Immunosuppression strategies after transplantation according to the immunological risk. While the immunological risk decreases over time after the first year post-transplant period, sparse prospective data for maintenance phase are available to guide the immunosuppression minimization strategy. Fourfold includes antithymocyte globulins or anti-CD25 monoclonal antibody for induction, plus three maintenance drugs, for example, calcineurin inhibitors (e.g., tacrolimus or cyclosporine), steroids (e.g., methylprednisolone or prednisolone), and antimetabolite (mycophenolate mofetil or mycophenolate sodium) or mTor Inhibitor (sirolimus or everolimus). During early maintenance therapy, calcineurin inhibitors and steroids are tapered down. According to the transplant center strategy and individual risk profile, one maintenance drug is eventually discontinued and patients continue on long-term twofold drug therapy (e.g., CNI plus antimetabolite, CNI plus mTor inhibitor, CNI plus steroids).

CNI monotherapy. Such minimization strategies aim to reduce long-term drug-specific side effects to improve individual tolerability and adherence. Nevertheless, it is unclear today whether they influence long-term outcomes.

Side effects of current immunosuppressive drugs

As pointed out, the frequent side effects of immunosuppressants remain an important clinical problem, which also negatively influence long-term success after transplantation.

Cyclosporine causes several important side effects such as hypercholesterolemia, hypertension, gingival hypertrophy, constipation, hirsutism, acne, and nephrotoxicity [15–17]. Drug monitoring is mandatory because of its narrow therapeutic window and the potential for drug-to-drug interaction (i.e., modification of the effect of a drug when administered together with another drug). Tacrolimus is a more powerful CNI, with a more potent prophylaxis of rejection [1,16,18]. However, its use is associated with diabetes [19,20], neurological side effects (tremor, headache), hair loss, gastrointestinal side effects (e.g., diarrhea, nausea, vomiting), and hypomagnesemia [16]. In combination with mycophenolate, it also more often causes overimmunosuppression, namely polyoma nephritis [21–24]. For the same pharmacological reasons as cyclosporine, tacrolimus should be monitored using trough levels, which provide a reasonable estimate for exposure [25].

The mycophenolates, mycophenolate mofetil (MMF), and enteric-coated mycophenolate sodium (EC-MPS) [26–28] are based on mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH). Although not nephrotoxic, they inhibit, however, bone marrow function and cause gastrointestinal symptoms. Diarrhea is frequently observed under mycophenolates and a systematic work-up should be done before dose is reduced. Approximately 50% of patients with diarrhea experience resolution of their symptoms without dose adjustments [29–31]. Other MPA-associated side effects include the potential for overimmunosuppression, especially a higher incidence of CMV infections with more severe CMV disease, and a higher incidence of polyoma nephropathy, especially in combination with tacrolimus [21,22]. Regular monitoring for BK virus is recommended in such combinations. Furthermore, either CMV prophylaxis or a tight preemptive strategy with regular screening for CMV viremia should be instituted according to guidelines [32]. However, the recommended antiviral medications (e.g., valganciclovir) have their own toxicity (e.g., neurotoxicity, nephrotoxicity, and most importantly bone marrow toxicity), which contribute to the overall side effect burden.

Steroids have been part of the immunosuppressive regimens over the last 50 years [12,33] and are still initial standard worldwide. However, steroids have a large number side effects (weight gain, hyperglycemia/diabetes, osteoporosis, aseptic necrosis, hypertension, hyperlipidemia, growth retardation, cataracts, cosmetic: cushing, hirsutism, skin atrophy), especially with long-term use.

The immunosuppressants, sirolimus and everolimus [34,35], inhibit the mammalian target of rapamycin (mTor) and suppress lymphocyte proliferation and differentiation. Side effects [14,34,36,37] include dose-dependent bone marrow toxicity, hyperlipidemia, edema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility [38]. When combined with CNIs, pneumocystis prophylaxis is mandated, for example, low-dose cotrimoxazole. Emerging side effects including proteinuria, development of HLA antibodies [4], ovarian toxicity [39], and infertility warrant more research and a cautious individual approach. Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions.

Hence, it is obvious that drug toxicity is an imminent, frequent, and important problem, both for the patient and the physician. Current protocols aim to reduce such immunosuppressant-specific side effects using a synergistic regimen, and over the last two decades, successful minimization strategies clearly reduced side effect burden and resulted in better outcomes. In daily practice, overimmunosuppression, poor side effect profile remain frequent problems. In many instances, those dose adjustments are erratic and with only limited evidence. Obviously, prevention is better than treatment, which also applies for many side effects of immunosuppressants. Thus, a proactive and controlled minimization strategy will not only reduce dose-dependent side effects but also avoid drug-associated morbidity, diagnostic work-up, and costly co-medication in some individuals.

Current problems

Despite dramatic reduction in rejection rates, long-term graft attrition rates have not improved [40]. Risk for graft loss beyond the first year is even higher compared to 20 years ago, most likely due to the acceptance of more marginal donors and recipients. The two main reasons for graft loss remain death with a functioning graft and chronic allograft dysfunction [41,42] (Fig. 2).

Immunosuppression and death with a functioning graft

Although the restoration of kidney function dramatically reduces cardiovascular mortality and morbidity, RTR remain at high risk of death with a functioning graft when compared to the general population. The first causes are cardiovascular diseases, infections, and cancer [43].

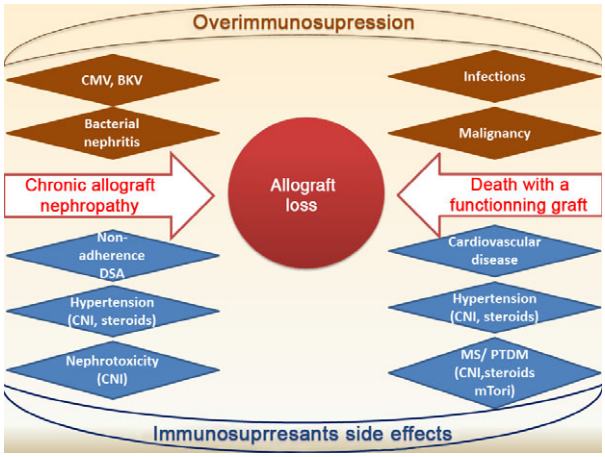

Figure 2 Main reasons of allograft loss: summarized concerns of over-immunosuppression and immunosuppressants side effects on allograft outcome. CMV, cytomegalovirus; BKV, polyoma virus; DSA, donor specific antibodies; MS, metabolic syndrome; CNI, calcineurin inhibitors; mTori, mammalian target of rapamycin inhibitors; PTDM, post-transplant diabetes mellitus.

Cardiovascular disease and metabolic disorders

Sarnak *et al.* [44] reported that cardiovascular death was 50-fold higher in RTR than in the general population. Kasiske *et al.* [45] demonstrated a higher risk for myocardial infarction during the first year following renal transplantation compared to patients remaining on the transplant waiting list. The excessive prevalence of traditional cardiovascular risk factors (hypertension, diabetes, obesity, smoking, and hypercholesterolemia) only partly explains this high cardiac mortality. Ojo [46] showed that, after renal transplantation, the frequency of some traditional cardiovascular risk factors remains stable; however, other important risk factors such as diabetes, hypercholesterolemia, and obesity are increasing. Post-transplant diabetes mellitus (PTDM) and metabolic syndrome in RTR are highly associated with the occurrence of cardiovascular events [47,48]. Yet, these factors do not completely explain this excess death rate. The cardiovascular risk scores developed for general population, as the Framingham equation, fail to predict the coronary risk of RTR [49]. Thus, other nontraditional risk factors have been identified and some are directly related to allograft function as proteinuria [50] and glomerular filtration rate (GFR) [51–53]. The restoration of renal function after kidney transplantation is key for cardiovascular patient survival. Conversely, patients who return to dialysis experience again much higher death rates and cardiovascular events [54].

These observations show the utmost importance to reduce modifiable traditional cardiovascular risk factors and to preserve renal function. The cardiovascular side effects of most immunosuppressants contribute to increased cardiovascular morbidity and mortality [55,56]. CNIs are nephrotoxic and cause hyperlipidemia, hypertension, and diabetes, mTor inhibitors favor hyperlipidemia, anemia, and proteinuria, while corticoids induce diabetes, hyperlipidemia, and obesity. However, effective rejection prophylaxis with these drugs will preserve renal function, which is also crucial for long-term outcome despite elevated cardiovascular risk factors. Nevertheless, it is evident that these risk factors (such as diabetes and hyperlipidemia) are associated with inferior outcomes after transplantation. All these concerns can be addressed by minimization or withdrawal strategies, as side effects are generally dose dependent.

Cancer and infections

Taken together, malignancies and infections are the leading cause of death with a functioning graft [57] and are clear symptoms of overimmunosuppression [58]. These unspecific side effects of all immunosuppressants are directly related to their immunosuppressive effects, the combination therapy with other immunosuppressants, and the cumulative immunosuppressive burden over time. While infectious deaths were decreasing over the last decades (eventually due to better diagnostics and medications), malignancies-related death was increasing. In addition, new infections such as BKV infections became prominent with current potent immunosuppression. This highlights the need for adequate immunosuppression, which is more than excellent rejection prophylaxis in the first months after transplantation. Opportunistic infections (e.g., CMV-, BKV, PCP-infections) are frequently observed in the first year after transplantation [59]. Risk factors for these infections were identified and successful prophylaxis strategies developed, decreasing the morbidity and mortality. Malignancies occur late after transplantation and are associated with increasing age and cumulative immunosuppression. Regular screening could be helpful, although it is unclear to what extent [58,60,61].

Immunosuppression and chronic allograft dysfunction

Chronic allograft dysfunction (CAD) (previously called "chronic rejection" or "chronic allograft nephropathy" and today called "Interstitial Fibrosis/Tubular Atrophy (IF/TA)" in renal biopsy) remains the main obstacle for long-term success [62]. Biopsy shows rather unspecific nephron damage and nephron loss, attributed to immunological (e.g., HLA antibodies) and nonimmunological factors such as donor factors (e.g., age, brain death, pre-existent disease), ischemia-reperfusion injury, recipient factors (e.g., hypertension, diabetes), infection (e.g., polyoma virus

(BKV), CMV, recurrent bacterial interstitial nephritis), and drug toxicity (e.g., CNI-associated nephrotoxicity) [62–65]. Potentially modifiable factors for CAD are CNI nephrotoxicity, hypertension, infections [62], which are directly associated with overimmunosuppression or too high drug exposure. The exact contribution of the different factors is under discussion [66] and may vary between populations and over time. Other frequently observed side effects (e.g., cosmetic side effects, neurotoxicity, gastrointestinal toxicity) lead to multiple medical problems, additional co-medication and diagnostics, increasing costs, and nonadherence [67,68]. Contrary to the many and frequent side effects, late acute rejections are infrequent [69] and are mostly due to nonadherence [67], indicating that current maintenance therapy—if taken adequately—is extremely efficient to prevent acute rejection.

Despite frequently observed overimmunosuppression and effective prevention of acute rejection, some patients, especially those with a high immunological risk, experience acute ABMR episodes or develop de novo HLA antibodies. This suggests that current immunosuppressive therapy has only limited efficacy in preventing B-cell-mediated immune responses, while being very effective in preventing acute T-cell-mediated rejection. All ABMR remains an imminent threat to the graft [70], mainly due to poor treatment options [71]. Chronic humoral injury is considered a major reason for late graft loss. Unfortunately, our knowledge about development of de novo HLA antibodies is limited, and data on different immunosuppressive drugs on the humoral immune system are sparse. The development of HLA antibodies has been associated with underimmunosuppression; however, it is completely unknown whether an increase of immunosuppression will decrease this development or only increases side effects and subsequently nonadherence. Nonadherence is a frequent identified cause for HLA antibodies, but is rather associated with immunosuppressive side effects or with complex and inconvenient dosing schemes. Future research including the development of novel immunosuppressants is needed to address the imperfect suppression of the humoral response under current immunosuppressants. Additionally, novel strategies including the development of better tolerable and convenient drug regimens are needed to improve adherence.

CNI-related nephrotoxicity is one of the predominant nonimmunological factors for CAD [15,42]. Evidence is coming from non-RTR; more than 30% of patients are experiencing severe renal dysfunction after 10 years of CNI treatment [72]. Almost 10% of transplant recipients of a nonrenal allograft experience ESRD after 10–15 years. As most RTR receive only one more or less damaged kidney, it seems likely that chronic CNI-associated toxicity also contributes significantly to chronic allograft dysfunction after kidney transplantation, although the exact amount is under discussion [66].

Other factors linked to immunosuppressants and overimmunosuppression, such as hypertension, diabetes, and infections, contribute to CAD [62,73]. In practice, it is difficult to distinguish between the different factors contributing to CAD in kidney biopsies because all these factors are more or less present in the same patients. They will lead to nephron injury and ultimately nephron loss. In this context, it is conceivable that HLA antibodies are causing more nephron injury in the presence of metabolic disturbances, hypertension, glomerular hyperfiltration, and CNI-associated vasoconstriction with latent glomerular ischemia.

As immunosuppressive efficacy has improved, the goals that define optimal immunosuppressant choices have changed. Thus, the main focus today is to improve transplant and patient long-term outcomes, which are strongly dependent on the reduction of immunosuppressant toxicity in combination with better prophylaxis of humoral immune responses.

Current strategies of immunosuppression minimization

In summary, most major causes for the lack of improvement of long-term allograft survival are directly or indirectly related to the side effect burden of current immunosuppressive regimens (e.g., nephrotoxicity, metabolic, and cardiovascular side effects, nonadherence) [57,65,68,73] or are related to overimmunosuppression [46,58,63]. In contrast, acute rejection in maintenance patients is rare [69], and currently, there is no evidence that increased standard immunosuppression will lead to less chronic humoral rejection. Thus, there is a clear medical need to further explore strategies to minimize immunosuppression exposure, especially in patients on standard maintenance therapy. Such minimization or withdrawal protocols have to be tested in rigorous clinical trials in comparison with standard therapy in order to provide a robust scientific basis for improved future drug regimens.

Corticoid minimization

There is a long history of steroid avoidance or withdrawal in transplantation [74–83]. Most practitioners still consider prednisolone to be a fundamental adjunct to primary immunosuppression, even though successful prednisolone withdrawal has been achieved in the vast majority of patients in many prospective, randomized trials [12,33,84]. These trials together with a meta-analysis suggest the risk of steroid withdrawal depends on the immunological risk (e.g., HLA mismatch, ethnicity), on the concomitant immunosuppressive medication, and on the time after

transplantation. For steroid avoidance, a potent induction agent has to be used, which, however, cause some other unwanted effects and still results in a slightly higher rejection rate. Although the risk of rejection diminishes over time, potential benefits are less prominent after a prolonged steroid treatment period. Some papers [85,86] call for a cautious approach in patients with IgA nephropathy, although recurrence rates under current standard therapy with tacrolimus and IL-2R induction were very low and overall long-term outcome of steroid-free patients were excellent. In summary, steroid-free or steroid withdrawal protocols are safe and feasible with modern immunosuppression, and it is well documented that the combination of MPA plus CNI allows a safe steroid-free maintenance therapy in the majority of patients. The best strategy is not clear yet, and more data on the long term would be useful to address the safety of steroid-free protocols. Obviously, most patients benefit from a steroid-free maintenance therapy with a reduction of associated side effects, including cardiovascular risk factors.

CNI minimization and withdrawal

In maintenance patients, the potency of IL-2R antibodies, MPA, or mTor inhibitors can be used for substantial dose reductions of nephrotoxic CNIs. As pointed out by Kamar *et al.* [87] in this issue, MPA-based minimization leads to better renal function [34,35,88,89]. Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first 3 years has been associated with an increased rejection risk and worse outcomes in prospective randomized studies [90,91]. In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond 5 years' post-transplant and resulted in improved renal function [92,93]. This observation highlights the decreasing rejection risk over time and provides a good example of a time-dependent minimization strategy.

In addition, recent studies suggest that mTor inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favorable side effect profile [8].

As further discussed by Diekmann [94], many studies observed that mTor inhibitors can replace CNIs at later stages, for example, 3–6 months after transplantation, with significant improvements in renal function despite slightly increased rejection risk. Late conversion to mTor inhibitors is less successful [95–97]. However, high discontinuation rates (around 35–40%), mostly due to side effects, offset some of the benefits [98]. Recent publications on higher rate of HLA antibodies under mTor therapy raised concerns [99]. Similarly, proteinuria and poor renal function are associated with inferior outcomes after conversion.

Due to an antiproliferative effect and a lower incidence of malignancy in sirolimus-treated patients, conversion from CNIs to mTor inhibitors could be beneficial for patients, who develop or are at a high risk for the development of post-transplant malignancy [100]. For patients with post-transplant Kaposi sarcoma, mTor inhibitors offer a successful and well-documented treatment option. Several controlled trials have reported less skin malignancies after conversion to mTor inhibitors [101,102]; however, high withdrawal rates limit its clinical use.

In summary, mTor inhibitors are a valid, safe, and well-documented alternative in case of severe side effects under standard therapy, including patients with skin tumors. Generally, late conversion in patients with poor renal function and/or proteinuria is more problematic, and a cautious and individual approach should be followed in those patients. Ongoing studies will help to better define the role of mTor inhibitors after transplantation in the near future.

Another option discussed by Grinyo is the potential opportunities with Belatacept, a promising new agent [103–112], with a complete new mechanism of action that allows a complete CNI-free immunosuppression, at least in low-risk patients.

Despite their side effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than 30 years because they have resulted in an exemplary improvement in kidney graft survival. Future protocols aim to minimize or even eliminate CNIs, and CNI therapy remains a delicate balancing act. However, until such strategies provide superior outcomes, CNIs remain the standard of care in the initial postoperative period. For severe CNI-related side effects, such as nephrotoxicity, CNI withdrawal, replacement, or profound, reduction is needed. Special attention should be paid to maintenance patients, which need less CNIs than previously thought [13,34,35,88,89]. It is important to note that CNIs maintenance does not influence other important factors such as adherence, recurrent disease, and chronic antibody-mediated rejection. The development of safe time-dependent CNI minimization or even withdrawal protocols in maintenance patients remains an important goal for the reduction of nephrotoxicity.

Conclusion

In the future, new immunosuppressive strategies should aim to reduce the side effects of current immunosuppressants, either by the clinical development of new more selective drugs with better tolerability or by the constant optimization of current treatment protocols. This should allow for a more efficient immunosuppression with far less side effects leading to significant improvements of long-term graft survival. Overimmunosuppression and drug-associated toxicities contribute to the cardiovascular risk

profile in most maintenance patients and to chronic allograft dysfunction. It is important to note that drug-associated side effects also contribute to nonadherence, which leads to the development of acute rejection or de novo HLA antibodies. Current immunosuppressive protocols are limited in their efficacy to prevent chronic antibody-mediated rejection and other factors aggravate antibody-mediated nephron injury. As a consequence, the reduction of side effects in combination with better prevention of HLA-antibody development is crucial for improving long-term outcomes.

This goal could be achieved by time-dependent and optimized immunosuppressive protocols, since rejection risk is decreasing over time, while side effects are increasing. The key for all future improvements, however, remains well-conducted and adequately powered clinical trials, which are necessary to provide a solid evidence basis for all these minimization strategies.

Funding

The authors have declared no funding.

Acknowledgements

KB has consultancy agreements with Bristol-Myers Squibb, Hexal, LifeCycle Pharma, Novartis Pharma, TCL Pharma and Pfizer and has received research grants for clinical studies, speaker's fees, honoraria, travel expenses, and payment for the development of educational presentations from AiCuris, Astellas, Bristol-Myers Squibb, Hexal, LifeCycle Pharma, Novartis Pharma, TCL Pharma, Roche AG, and Pfizer.

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