DOI:10.23873/2074-0506-2018-10-1-42-49

The basic principles of immunosuppressive therapy after kidney transplantation

D.N. Suslov

Russian Scientific Center of Radiology and Surgical Technologies n.a. Acad. A.M. Granov,

70 Leningradskaya Str., Pesochny settlement, St. Petersburg 197758 Russia

Correspondence to: Dmitriy N. Suslov, Cand. Med. Sci, Head of the Experimental Surgery Group, Russian Scientific Center of Radiology and Surgical Technologies n.a. Acad. A.M. Granov,

e-mail: susloff.dmit@yandex.ru

Received: 16 October 2017

Accepted for publication: 1 December 2017

The article deals with medical and organizational issues of individually-adapted immunosuppressive therapy in renal allograft recipients. In the recent years, the basis of nephroprotective therapy schemes includes m-TOR inhibitors. The accessibility of these drugs for those in need is limited. Meanwhile, a more widespread use of these drugs in clinical transplantation would both increase the life span of a transplanted kidney, and reduce the risk of viral infections and cancer in the long-term after kidney transplantation, and would also allow a rational use of budget funds for the treatment of such patients.

Keywords: immunosuppressive therapy, individual adaptation, accessibility, m-TOR inhibitors

Suslov D.N. The basic principles of immunosuppressive therapy after kidney transplantation. *Transplantologiya. The Russian Journal of Transplantation.* 2018;10(1):42–49. (In Russian). DOI:10.23873/2074-0506-2018-10-1-42-49

AEs – adverse events
CNIs – calcineurin inhibitors
MPA – mycophenolic acid
PEM – Provision of Essential Medicines

CsA – cyclosporine A

ECDs – expanded criteria donors
EVE – everolimus
GFR – glomerular filtration rate
IST – immunosuppressive therapy
SPP – Supplementary Pharmaceutical Provision
7CN – 7 Costly Nosologies
CSs – systemic corticosteroids
TAC tacrolimus

Postoperative immunosuppressive therapy (IST) is one of the important components of patient treatment by kidney transplantation. Such therapy is initiated as early as in the period of the recipient preparation for surgery in a number of cases and goes on for the entire period while the renal, hepatic, cardiac, pulmonary and other transplants, and transplanted complexes are functioning. i.e. actually for life. In the long-term the IST becomes the factor that largely determines the duration of the transplanted organ functioning and the recipient's lifetime [1].

Schematically, the IST from the time of surgery can be represented as a combination of the following drugs: selective immunosuppressants and/or interleukin inhibitor + calcineurin inhibitors (CNIs) + selective immunosuppressants or other immunosuppressants + systemic corticosteroids (CSs). That means, since the operation, the IST is four-component or, in some cases, a three-component one. After the patient discharge for an outpatient treatment, the IST is also a combined therapy, a three-component one in the overwhelming majority of cases. Its scheme is almost the same as in the early postoperative period: CNIs in combination with selective immunosuppressants or other immunosuppressive agents, and systemic corticosteroids. Further, the IST may vary depending on the transplanted organ and recipient condition. The set of drugs remains virtually unchanged throughout the whole period of the graft functioning. The therapy components may be changed only if there are strictly defined

medical indications. As already mentioned, three-component schemes are the most often used; more rarely, a two-component therapy or monotherapy is chosen. The proportion of patients with a functioning renal transplant receiving a two-component IST in St. Petersburg makes 14.1% (the data as of early 2017). Monotherapy is used mainly in the patients with a functioning hepatic graft.

Of the schemes used, the most widespread in recent years has been a scheme that includes various dosage forms of CNI Tacrolimus (TAC), one of mycophenolic acid (MPA) drugs, and CSs (or no CSs). The similar therapy is used after the discharge from hospital in 59.42% of patients; another CNI, cyclosporine A (CsA), is used in 35.68% of patients in combination with one of MPA drugs; and only in 4.9% of patients we can refuse from using CNI.

Table 1 presents the drugs used for IST in the Russian Federation and their profiles of adverse events (AEs) [2-4].

Table 1. A semi-quantitative comparison of adverse effect profiles of immunosuppressants

AE / Medication	CsA	TAC	MPA	Azathioprine	Belatacept	CS	m-TOR inhibitors
Nephrotoxicity	+++	+++	–	–	–	–	–
Neurotoxicity	++	+++	–	–	+	+	–
Hypertension	+++	++	–	–	–	+++	–
Hyperlipidemia	++	+	–	–	–	++	+++
Diabetes	+	+++	–	–	–	++	– +
Hepatotoxicity	+	+	–	+	–	–	+
Gingival hyperplasia	++	–	–	–	–	–	–
Hirsutism	++	–	–	–	–	+	-
Diarrhea	+	+	+++	+	++	–	+++
Leukopenia	–	–	+++	+++	+	–	+
Thrombocytopenia	–	–	+	+	+	–	++
Infections / PTLD *	+	+	+	+	+++	+	+

- *PTLD - Posttransplant lymphoproliferative disease

Table 1 clearly demonstrates the lack of an ideal drug, and, consequently, the lack of an ideal drug combination at present. All medicinal products have side effects or AEs. And moreover, the drugs belonging to different groups may have common AEs that can manifest themselves more likely in drug combinations.

The use of CNIs (CsA, TAC) made it possible to achieve a 90% of a 1-year graft survival, reduced the incidence of acute rejection to 5% in the early posttransplant period; however, their long-term use may cause serious AEs such as nephrotoxicity and hepatotoxicity arising regardless of the drug doses. That could explain only very slight improvements in the half life of a kidney graft in the long-term: from 6.8 years in 1989 to 8 years in 1995, and 8.4 years in 2000 [5-7].

In one of the authors' opinion, the IST main principle nowadays is its individual approach, i.e. when choosing the therapy scheme, it is necessary to consider all the advantages and disadvantages of the prescribed drugs in each individual patient [8]. However, the individual approach can be implemented only if the following criteria are met: the use of efficient and safe drugs with the therapy scheme being unchanged after the discharge from hospital, i.e. the continuity principle should be followed; and with this, the drug prescribed in the transplantation center should be available for the patient. Thus, the basic principles of IST by their priority can be listed as following:

1. Efficacy
2. Safety
3. Continuity
4. Availability
5. Individual approach

The efficacy and safety are the key principles, since almost all the regimens include drugs classified as drugs with a "narrow therapeutic range", or "critical dose" drugs (as in case of CsA and TAC) [1].

The efficacy and safety of drugs are defined in Article 4 of the Federal Law "On Circulation of Medicines": the safety of a medicine is the characteristics of a medicine based on a comparative analysis of its efficacy and assessment of health hazard. The efficacy of a medicinal product is the characteristics of the degree of positive effect of a medicinal product on the course of a disease [9]. In case of pharmacological therapy of an organ transplant recipient, the efficacy can be defined as the use of drugs or a drug combination that contribute to the achievement of the doctor's goal.

Continuity refers to the sequence order, substitution of drugs [10]. In our case, this implies the opportunity to continue treatment at the recipient's place of residence with the same medications (according the international nonproprietary name and trade name) that have begun the treatment at the transplantation center, the possibility of a safe substitution of one drug for another.

Availability derived from "available" i.e. uncovered, giving open access [10]. In our case, this implies the possibility for each individual patient to get a necessary medicine free, according to indications.

In 2011, the Federal Program for the Provision of Essential Medicines (PEM) was adopted. The Program pursued the following objectives: to develop the targeted social support system for the population; to establish a new procedure of financing the measures of social support for the categories of population entitled to special benefits; to implement measures aimed at improving the availability and quality of medical and medicinal care; to

implement the methods for standardizing medical care; to improve the control and supervisory activities [11]. The implementation of PEM Program provides the necessary drugs for patients receiving a lifelong IST. The medications required for therapy are given to the patients under the Program for Supplementary Pharmaceutical Provision (SPP) and "7 Costly Nosologies" (7CN) Program. The essential immunosuppressive drugs are included in the Russia's Essential Drugs List of 7CN Program. Under the SPP Program, it is possible to obtain drugs intended primarily for the treatment of IST-related complications. Meanwhile, under 7CN Program, 5 drugs are purchased, the mean price for 1 mg being 34.96 Roubles. According to SPP Program, the patients can obtain 6 drugs, the average price for 1 mg making 63.53 Roubles, while the cost of one prescription under "7 Costly Nosologies" Program, as determined by the Government of the Russian Federation, makes 30.095 Roubles, and 870 Rubles per month are allocated per patient from the Federal Budget for the implementation of the SPP Program.

It should be noted that the PEM Program was unable to ensure the individual approach of the IST. The implementation of the Program contributed to a gradual reduction in the share of original brand-name formulations and an increased number of generics on the market of pharmacological products for IST. Currently, under 7CN Program, patients can receive only 3 original brand-name drugs, while one original drug form can be used only in patients with substantiation of indications due to side effects of generics.

It is the use of generic immunosuppressive drugs and the increased number of expanded criteria donors (ECDs) that have raised the demand in

Russia in the IST schemes that would not have a detrimental effect on the transplanted kidney, i.e. nephroprotective IST schemes.

The following data deserve attention. Twelve months after the kidney transplantation, the MDRD-calculated glomerular filtration rate (GFR) makes 59.08 $\pm$ 18.91 mL/min/1.73 m^2 in the patients treated using the TAC + MPA $\pm$ CS scheme. In patients receiving the IST scheme based on CsA: CsA + MPA + CS, the GFR after 12 months was 62.43 $\pm$ 20.23 mL/min/1.73 m^2 . The proportion of patients with GFR <40 mL/min in those two groups was 16% and 26.92%, respectively. Compare: in 2 recipients operated on in 1987, and 1988 in whom CNIs were withdrawn after 18-24 months post-surgery, the GFRs (MDRD) at 27 and 28 years after kidney transplantation were 51.28 mL/min/1.73 m^2, and 61.24 mL/min/1.73 $m^{2,}$ respectively.

In addition, in the early and long-term periods after the kidney transplantation, the patient and his attending physician are facing some risks; the effect of IST, especially of some drugs used for therapy, increases in the long-term. If the main risks early after kidney transplantation include an acute renal graft rejection, delayed or reduced renal graft function, non-healing of the postoperative wound, then our therapy should prevent the development of rejection, neither exacerbating the existing graft function abnormalities nor impeding the graft function recovery [12]. The scheme using CNIs in combination with MPA agents and CS seems to be the most optimal in the early period after kidney transplantation. The risks at the long-term after kidney transplantation include, first of all, those associated with the use of nephrotoxic drugs, up to the development of interstitial fibrosis and tubular atrophy, the risks of development and progression of viral infection caused by cytomegalovirus, and the risk of cancer development [12]. Should one change therapy if there is the evidence of AEs or

complications? Certainly, we should. Is it necessary to prevent or delay the occurrence of these AEs and complications? Certainly, it is necessary. And here the two-stage IST scheme proposed by Spanish transplantologists [12] is becoming relevant implying the IST using CNIs in the early period, and nephroprotective schemes of IST in the long-term.

The components of nephroprotective regimens include the drugs from the group of the mammalian target of rapamycin (m-TOR) inhibitors. The m-TOR inhibition leads to an immunosuppressive effect, blocks the proliferation and angiogenesis, hinders the replication of cytomegalovirus, and, ultimately, prevents the development of chronic transplant nephropathy, and impedes the growth of tumor cells [13-19]. The m-TOR inhibitors are used in combination with CNIs and CS, without CNIs in combination with MPA salts and CS, allow an efficient and safe use of IST schemes without corticosteroids. The administration of m-TOR inhibitors is possible at different stages after transplantation: in combination with CNIs and CSs immediately after the surgery, maintaining low doses of CNIs in the period from 3 to 6 months after surgery, or with CNI withdrawal in case of indications to or possibilities of their withdrawal making an early conversion, or adding m-TOR inhibitors, in the IST scheme at any stage after surgery making a late conversion [20, 21]. The commercial availability of drugs of the m-TOR inhibitor group that allow an effective and safe use of new combinations of immunosuppressants, would serve a good basis for further activities on the individualized approach to IST.

Currently, an available drug from the m-TOR- inhibitor group is everolimus (EVE). The drug is included in the List of Essential Medicinal Products, as well as in the List of drugs that are purchased under the SPP Program. Sirolimus, another drug from this group, the first to appear on the

market and used in renal allograft recipients, has not been included in the List of vital drugs, its availability for patients is limited, it can be obtained only if there are medical indications and the wish and the will of the specialist who prescribes it. Meanwhile, EVE is the most expensive of immunosuppressive drugs, having the price of 292.67 rubles for 1 mg of the drug. The IST schemes using EVE are no more expensive than the schemes with traditionally used drugs. Data on monthly and yearly costs of treatment for renal allograft recipients are shown in Table 2.

Table 2. The cost of immunosuppressive therapy in the long-term after kidney transplantation

IST scheme	Cost of therapy (1 month), RUB	Cost of therapy (12 months), RUB
CsA + MPA + CS	15,880.46	190,565.52
TAC + MPA + CS	19,573.47	234,881.64
TAC (ext.release) + MPA + CS	20,701.91	248,422.92
EVE + CsA + CS	12,087.63	145,050.36
EVE + MPA + CS	25,509.56	306,114.72
EVE + TAC (ext.release) + CS	22,386.88	268,642.56

The data given in Table 2, clearly show that the individual approach to IST neither brings a significant increase in the cost of treatment of patients with functioning renal allograft, moreover, it allows a rational use of budget funds allocated for these purposes. The most expensive scheme has been EVE + MPA + CS, but the number of patients receiving such treatment is small. None of the schemes presented in Table 2 exceeds the cost of the prescription determined by the Government of the Russian Federation (the cost of one prescription = the cost of a monthly treatment). In the recent years in St. Petersburg, 16% of patients who underwent organ transplantation have been using m-TOR inhibitors. And only 40% of renal

transplant recipients among those receiving m-TOR inhibitors do not receive CNI, i.e. they are treated up to the scheme EVE + MPA + CS.

The m-TOR-inhibitor therapy-related AEs are mostly dose-dependent and respond well to pharmacological therapy or may be coped with after replacing one drug of the m-TOR-inhibitor group with another [12].

Non-compliance with the therapy regimen has been another significant problem in the long-term. Despite a high incidence of the drug withdrawal associated with side effects after the treatment initiation, a single dosing of the m-TOR inhibitor sirolimus may have a positive effect on the long-term compliance. There are scarce data on improving the compliance with the treatment regimen when taking a combination of sirolimus + TAC of extended release in a low dose [22].

Based on the available data, we can state that, although CNIs are efficient in minimizing the risk of acute graft rejection, their use is restricted by a number of factors. Immunosuppression regimes based on using sirolimus without CNI or with a lowered CNI dose allow the renal function to be better preserved, and the risk of neoplasms and infections to be considerably decreased [23]. CNIs represent the IST "gold standard" in the initial period, while the immunosuppressive maintenance therapy can be based on the m-TOR inhibitors: sirolimus and EVE [12, 21, 22].

In our opinion, the drugs of the m-TOR inhibitor group can and should be used: in patients with low or moderate immunological risk; in young patients to ensure a good long-term function of the kidney graft; in recipients older than 50 years who received grafts from the suboptimal donors having cardiovascular pathology, heart attacks, strokes, malignancies in the personal or family history, who have proteinuria lower than 0.8 g/day or no proteinuria, without marked abnormalities in serum lipids

(hypercholesterolemia not exceeding 9 mmol/L and hypertriglyceridemia not exceeding 8.5 mmol/L); patients with a body mass index of less than 35. When prescribing these drugs, one should mind the presence and severity of possible contraindications, such as proteinuria over 1 g/day, refractory dyslipidemia, recurrent or newly acquired glomerulonephritis, acute or chronic rejection, a planned surgical intervention or the presence of surgical wounds at healing stage, pregnancy or the patient's desire to get pregnant.

An individual approach to a lifelong IST acts as the main factor in the long-term after organ transplantation, which determines the span of graft functioning and, accordingly, recipient's lifetime. The individualized choice of IST for each particular patient should be based on medical criteria only, and a free access to of efficient and safe immunosuppressive drugs. An individual approach to drug therapy will help to optimize the expenses for the treatment and follow-up of organ transplant recipients in the long-term period after surgery, and to achieve their maximum medical and social rehabilitation.

Conclusions

1. An individually selected lifelong immunosuppressive therapy allows the maximum medical and social rehabilitation of organ transplant recipients to be achieved and the life span of the transplanted organ to be increased.

2. The individualized immunosuppressive therapy is possible only with the availability of effective and safe drugs in a free access.

3. There is still no "ideal" immunosuppressive drug or "ideal" IST scheme. The "ideal" scheme of immunosuppressive therapy can only be the one that has been individually adapted for each particular patient.

4. The choice and combination of drugs for immunosuppressive therapy should be determined only by the indications and contraindications to their use. The cost and other "non-medical" factors should only be taken into account, and not determine the appropriateness of using the drug in clinical practice.

5. All immunosuppressive drugs authorized by the country must be listed as "vital medicines", it is advisable to purchase all drugs for a continuous high-tech treatment at the expense of a single source of finance.

6. An individualized approach to drug therapy will allow the optimization of all expenses for the treatment and follow-up of patients in the long-term after transplantation surgery.

Conflict of interests. Authors declare no conflict of interest.
Financing. The study was performed without external funding.

References

1. *Drug monitoring and interchangeability of original and generic, immunodepressive drugs with narrow therapeutic index*. National clinical guidelines. Moscow, 2014. 23 p.

2. Kuypers D.R. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Saf.* 2005;28(2):153–181. PMID:15691225

3. Halloran P.F. Immunosuppressive drugs for kidney transplantation. *N Engl J Med.* 2004;351(26):2715–2729. PMID:15616206 DOI:10.1056/NEJMra033540

4. Heemann U., Viklicky O. The role of belataceptin transplantation: results and implications of clinical trials in the context of other new biological immunosuppressant agents. *Clin Transplant*. 2013;27(1):E3-11. PMID:23199344 DOI:10.1111/ctr.12044

5. Opelz G., Dohler B. Influence of Immunosuppressive Regimens on Graft Survival and Secondary Outcomes after Kidney Transplantation. *Transplantation*. 2009;87(6):795–802. PMID:19300179 DOI:10.1097/TP.0b013e318199c1c7

6. Morris P.J. Transplantation – a medical miracle of the 20th century. *N Engl J Med*. 2004;351(26):2678–2680. PMID:15616201 DOI:10.1056/NEJMp048256

7. Campbell S., McDonald S., Chang S., et al. Chapter 8. Transplantation. In: McDonald S., Chang S., Excell L., eds. *ANZDATA registry report 2007*. Adelaide, South Australia: Australia and New Zealand Dialysis and Transplant Registry, 2007.

8. Jain K.K. From molecular diagnostics to personalized medicine. The IBC Workshop, London, UK, 1st May, 2002. *Exp Rev Mol Diagn*. 2002;2(4):299–301. DOI:10.1586/14737159.2.4.299

9. On the circulation of medicines. Federal Law of 12.04.2010, № 61FL. November 25, 2013 ed. Available at: https://normativ.kontur.ru/document?moduleId=1&documentId=304074

10. Dal' V.I. Explanatory dictionary of the living Great Russian language: in 4 volumes. Moscow: Russkiy yazyk Publ., 1978-1980.

11. Yurgel' N.V., Tel'nova E.A. ADS – PNM, "7 nosologies," and then what? *Vestnik Roszdravnadzora*. 2008;(5):4–21. Available at: http://www.remedium.ru/public/journal/vr/2008/VR_05_2008.pdf

12. Pascual J., Boletisb J.N., Campistolc J.M. Everolimus (Certican) in renal transplantation: a review of clinical trial data, current usage, and future directions. *Transplant Rev*. 2006;20(1):1–18. DOI:10.1016/j.trre.2005.10.005

13. Ormiston J.A., Serruys P.W., Regar E., et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB) a prospective open-label trial. *Lancet*. 2008;371(9616):899–907. PMID:18342684 DOI:10.1016/S0140-6736(08)60415-8

14. Ponticelli C. Can mTOR inhibitors reduce the risk of late kidney allograft failure? *Transpl Int*. 2008;21(1):2–10. PMID:17635837 DOI:10.1111/j.1432-2277.2007.00524.x

15. Cruzado J.M. Nonimmunosuppressive effects of mammalian target of rapamycin inhibitors. *Transplant Rev*. *(Orlando)*. 2008;22(1):73–81. PMID:18631860 DOI:10.1016/j.trre.2007.09.003

16. Contreras A.G., Dormond O., Edelbauer M., et al. mTOR-understanding the clinical effects. *Transplant Proc*. 2008;40(10 Suppl):S9-S12. PMID:19100913 DOI:10.1016/j.transproceed.2008.10.011

17. Hudes G.R. Targeting mTOR in renal cell carcinoma. *Cancer*. 2009;115(10 Suppl):2313–2320. PMID:19402072 DOI:10.1002/cncr.24239

18. Eisen H. Long-term cardiovascular risk in transplantation--insights from the use of everolimus in heart transplantation. *Nephrol Dial Transplant*. 2006;21(Suppl 3):iii9-13. PMID:16815858 DOI:10.1093/ndt/gfl295

19. Schuler W., Sedrani R., Cottens S., et al. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. *Transplantation*. 1997;64(1):36–42. PMID:9233698

20. Guba M., Pratschke J., Hugo C., et al. Early conversion to a sirolimus-based, calcineurin-inhibitor-free immunosuppression in the SMART trial: observational results at 24 and 36months after transplantation. *Transplant Int*. 2012;25(4):416–423. PMID:22320241 DOI:10.1111/j.1432-2277.2012.01432.x

21. Guba M., Pratschke J., Hugo C, et al. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal transplant patients: one-year analysis of a randomized multicenter trial. *Transplantation*. 2010;90(2):175–183. PMID:20463641 DOI:10.1097/TP.0b013e3181e11798

22. Jun H., Kim M.G., Jung C.W. Clinical advantages including medication adherence with conversion to once-daily advagraf and sirolimus combination in stable kidney recipients. *Int J Clin Pharmacol Ther*. 2016;54(2):81–86. PMID:26709601 DOI:10.5414/CP202518.

23. Hariharan S., McBride M.A., Cherikh W.S., et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int*. 2002;62(1):311–318. PMID:12081593 DOI:10.1046/j.1523-17