Comparative Study: Mtor Inhibitors Versus CNI In Kidney Transplant Recipient In Patients Attending Minia Nephrology& Urology University Hospital

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ABSTRACT

Long-term CNI exposure may induce irreversible nephrotoxicity, resulting in progressive graft dysfunction. The CNI can also promote cardiovascular events and malignancies, which are the leading causes of premature death with a functioning graft. This discrepancy has prompted investigations into CNI retention strategies, which maintain adequate immunosuppressive effects without compromising safety Mammalian target of rapamycin inhibitors (mTORi) are new immunosuppressants that exhibit little or minimal nephrotoxicity. The dual immunosuppressive and antineoplastic properties of mTORi offer a distinct advantage for this class of drugs in the treatment of patients who receive kidney transplant. Nevertheless, major concerns associated with the *de novo* introduction of mTORi include the risk of AR, impaired wound healing, and prolonged delayed graft function (DGF), limiting the adoption of mTORi as a first-line immunosuppressant. The current state of the art with mTORi is the quest to discover the optimal immunosuppressive schedule that could guarantee kidney transplant recipients the lowest incidence of rejection and the best safety and long-term renal function. Thanks to all the basic, translational and clinical research achieved in the last twenty years, we now use mTORi as de novo immunosuppression in association with CNI at trough levels of 3–8 ng/mL. Another possibility is represented by the conversion of either CNI or mycophenolate (MPA) to an mTORi later on after transplantation. This can be beneficial in cases in which CNI- or MPA-related toxicity are evident, such as nephrotoxicity, tremor, leucopenia, diarrhea or CMV replication, which warrant a change in the immunosuppressive schedule.

Keywords: Mtor Inhibitors, CNI, Kidney Transplant Recipient.

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INTRODUCTION

Transplantation is the renal replacement therapy of choice for patients with end stage renal disease (ESRD). However, not all patients are suitable candidates for transplantation, and suitability is often determined by the risks of receiving graft versus the risks of not receiving a graft.[1]

Immunosuppressive therapy after kidney transplantation is based on calcineurin inhibitors (CNI). In most cases CNI therapy is combined with mycophenolate and steroids. In spite of good short-term results this therapy is associated with long-term toxicities, graft loss and patient death. Therefore, alternative immunosuppressive strategies are needed that combine excellent efficacy with low incidences of long-term adverse outcome.[2]

The mammalian target of rapamycin (mTOR) inhibitor class of immunosuppressive drugs were introduced more than 15 years ago as a new opportunity to create selective antirejection therapy in solid organ transplantation. In particular, absence of early nephrotoxicity seemed to provide an important opportunity to minimize or replace the calcineurin inhibitor (CNI) drugs, which were plagued by progressive nephrotoxicity when administered at doses needed to prevent rejection.[3]

Kidney transplantation

Kidney transplantation is the most commonly performed vascularized solid organ transplant. Technically, it is perhaps the easiest transplant procedure to perform and has the added security of the ability to provide dialysis in patients who experience delayed allograft function. However, it is unforgiving of technical error and can present specific challenges in the case of particular recipient or donor issues.[4]

Anatomy and Physiology

The kidneys are one of the paired retroperitoneal organs in the body. The diaphragm abuts the kidneys superiorly and posteriorly, along with the 12th rib. The right kidney is bordered by the right colonic flexure, liver (hepatorenal ligament), duodenum, and head of the pancreas anteriorly. The left kidney is bordered by the colon's splenic flexure, the splenic vessels, and the pancreas anterosuperiorly. The left kidney also shares a relationship with the spleen, which is anteromedial and connected via the lienorenal ligament. Inferoposteriorly, both kidneys lie on and

adjacent to the psoas muscle medially. The upper pole of both kidneys includes the adrenal glands.[4]
The renal arteries come directly off of the aorta laterally just below the takeoff of the superior mesenteric artery to supply each kidney. The right renal artery traverses behind the inferior vena cava. The renal artery then divides into its anterior and posterior divisions. The anterior division supplies 75% of the blood to the kidney, and the posterior division supplies 25%.[5]

Indications

Indications for kidney transplantation include chronic kidney disease (CKD) and renal tumors. Studies show that kidney transplantation prolongs patient lifespan compared with dialysis. Although perhaps only 25% of adult patients on dialysis are being referred for transplant evaluation (probably 95% of pediatric patients with ESRD will be referred), the number of potential candidates has resulted in burgeoning waitlists and longer waiting times for patients in need of kidney transplants.[4]

LIVING RENAL DONOR SELECTION

The generally accepted contraindications for living renal donation include reduced renal function, coercion, children below legal adulthood, hypertension, renal disease, malignant or infectious disease transmissible to a recipient, diabetes mellitus, significant cardiopulmonary disease, and significant urolithiasis.[4]

RECIPIENT PREPARATION

A Charlson comorbidity score that includes age is simple to calculate for a patient and can be used to help select an ESRD management option.[6]

Techniques

Skin preparation and incision

All the dissections should be accompanied by strict hemostasis and avoiding extreme injury to the abdominal wall muscles to simplify the future abdominal wall repair at the end of the procedure. All the bleeding sites should be completely hemostatized during this time because at the end of the procedure hemostasis will be very difficult. Also most renal failure patients has bleeding tendency due to platelet dysfunction specially in the first 2 hours after the hemodialysis or in those patient who underwent preemptive renal transplantation. If hemostasis is not complete wound or peri-graft hematoma is inevitable which will lead to the other complications such as infection, dehiscence, hydronephrosis or kidney compartment syndrome due to compression to the graft.[7]

Vascular anastomosis

The principles of vascular anastomosis are not different from any standard vascular surgery. The best suture size is usually 5-0 and 6-0 Prolene® sutures for venous and arterial anastomosis. The size of the needles depends of the location of the anastomosis but in most cases the needle should be taper-point or taper-cutting-tip round-bodied 3/8 circle with 11 – 13 mm length for better performance. For smaller arteries 7-0 or 8-0, 1/2 circle, 7-9.3 mm needles may be more suitable. For severe atherosclerotic arteries use of special visible Ethicon Visi-Black® Everpoint®, or Tapercut® needles with spatulated heads which is more firm and crash-resistant is needed.[8]

Urinary reconstruction

After completing the reperfusion stage usually the urine flow is started. Sometimes, especially in case of deceased donors or when the nephrectomy has been performed with difficulty in the living donors, the urine flow will be delayed. If the color and contour of the graft look good and the arterial and venous flow is good with a well-palpable thrill in the hilum, the surgeon should proceed to urinary reconstruction.[8]

Complications

Problems after a transplant may include.[9]
Post operative complications, such as bleeding, infection, vascular thrombosis and urinary complications

- Transplant rejection (hyperacute, acute or chronic)
- Infections and sepsis due to the immunosuppressant drugs that are required to decrease risk of rejection
- Post-transplant lymphoproliferative disorder (a form of lymphoma due to the immune suppressants). This occurs in about 2% of patients, occurring especially in the first 2 years post-transplant
- Skin tumours
- Imbalances in electrolytes including calcium and phosphate which can lead to bone problems
- Proteinuria
- Hypertension
- Recurrence of original cause of kidney failure
- Other side effects of medications including gastrointestinal inflammation and ulceration of the stomach and esophagus, hirsutism (excessive hair growth in a male-pattern distribution) with ciclosporin, hair loss with tacrolimus, obesity, acne, diabetes mellitus type 2, hypercholesterolemia, and osteoporosis.

Immunosuppression after renal transplantation

Induction therapy

Basiliximab

Basiliximab (Simulect, Novartis Pharmaceuticals) is a monoclonal antibody that acts as an interleukin-2 receptor antagonist. It has a marketing authorisation in the UK for the prophylaxis of acute organ rejection in adults having a kidney transplant. The summary of product characteristics states that basiliximab is to be used concomitantly with ciclosporin for microemulsion- and

corticosteroid-based immunosuppression, in patients with panel-reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.[10]

Maintenance therapy

Mycophenolate is the first-line antimetabolic agent as it was shown to be superior to azathioprine in preventing acute rejections with fewer side effects.[11]

Most centers switch from MMF to EC-MPS in case of gastrointestinal side effects or generally prefer EC-MPS rather than MMF, which are similar in efficacy and safety. Mycophenolate is generally avoided in female recipients of childbearing age without sufficient contraceptive measures, whereas a dose reduction is mostly sufficient in other complications such as viral infections.[12]

Mammalian target of rapamycin (mTOR) inhibitors in kidney transplantation

Mammalian (mechanistic) target of rapamycin (mTOR) inhibitors

There are three commercially available mammalian (mechanistic) target of rapamycin (mTOR) inhibitors the US Food and Drug Administration (FDA) approved in the United States: sirolimus, everolimus, and temsirolimus. Sirolimus (rapamycin) is a macrocyclic triene antibiotic that is produced by fermentation of *Streptomyces hygroscopicus*. Sirolimus was discovered from a soil sample collected in Rapa Nui, which is also known as Easter Island. Although it was originally developed as an antifungal agent, it was later found to have immunosuppressive (US FDA approval in 2003 for prevention of acute rejection in kidney transplantation) and antiproliferative properties that may be useful to treat or prevent proliferative diseases such as tuberous sclerosis, psoriasis, and malignancy.[13]

Mechanism of action

Following entry into the cytoplasm, sirolimus and everolimus bind to the FK binding protein and presumably modulate the activity of the mTOR. The mTOR inhibits interleukin (IL)-2-mediated signal transduction, resulting in cell-cycle arrest in the G1-S phase.[14]

Administration

Sirolimus – Sirolimus is typically administered as a tablet, although a solution is available for those who are not able to swallow.[15]

Dose

Clinical trials of initial immunosuppressive regimens after kidney transplant have included sirolimus as a component of a regimen that includes cyclosporine and glucocorticoids. In these trials, a one-time loading dose of 6 or 15 mg (three times the maintenance dose), followed by a maintenance dose of either 2 or 5 mg/day, was utilized.[16]

Dose adjustments

In clinical practice, dose adjustments for sirolimus and everolimus are made based upon several factors including concomitant administration of P450 enzyme inducers or inhibitors, hepatic insufficiency, toxicity, and/or infection. Dose adjustment of sirolimus is not required in the presence of kidney function impairment. By contrast, dose reductions of approximately one-third the normal maintenance dose should be used for patients with hepatic impairment.[17]

Drug monitoring

An excellent correlation exists between trough whole-blood levels and the area under the time-concentration curve (AUC) for sirolimus and everolimus. Routine therapeutic drug monitoring of sirolimus and everolimus blood concentrations is recommended for all patients.[18]

Steady-state concentrations

Steady-state concentrations of sirolimus occur five to seven days after initiation of therapy or a change in dose. During clinical trials, mean sirolimus whole-blood trough concentrations (determined by immunoassay) were 9 ng/mL (range, 4.5 to 14 ng/mL) and 17 ng/mL (range, 10 to 28 ng/mL) in the 2 and 5 mg treatment groups, respectively. Steady-state concentrations of everolimus occur after four to five days in kidney transplant patients receiving 0.75 mg twice daily.[19]

PHARMACOKINETICS

Absorption

Peak concentration — The time to peak concentration of sirolimus and everolimus is one to two hours. Bioavailability — The mean bioavailability of sirolimus oral solution is 14 percent. When compared with the oral solution, sirolimus tablets have a 27 percent higher bioavailability. The rate and extent of oral absorption of sirolimus may be reduced in Black patients.[20]

Distribution

The mean volume of distribution of sirolimus is 12 L/kg, with 97 percent of the agent being bound to albumin. The highest concentration of sirolimus is found in red blood cells (95 percent). This is followed by plasma (3 percent), lymphocytes (1 percent), and granulocytes (1 percent); usual blood/plasma ratios are approximately 30. In animal studies, high concentrations have been found in heart, intestines, kidneys, liver, spleen, muscle, lungs, and testes. Tissue/blood ratios have usually been >20.[21]

Metabolism

Sirolimus and everolimus are extensively metabolized in the liver and are substrates for cytochrome P450 3A4 and P-glycoprotein. The extent of metabolism of sirolimus in the intestinal wall is unknown. Sirolimus is countertransported in the gut lumen by P-glycoprotein. These processes account for low bioavailability and high

pharmacokinetic variability. Metabolites contribute to <10 percent of immunosuppressive activity of the parent compound, sirolimus. Known metabolites include hydroxy sirolimus, desmethyl sirolimus, and hydroxymethyl sirolimus. Everolimus, the 40-O-(2 hydroxyethyl) derivative of sirolimus, has six predominant metabolites, all with minimal immunosuppressive activity.[11]

Excretion

Total body clearance of sirolimus is 127 to 240 mL/hour/kg. Large intersubject variability occurs in the oral clearance of sirolimus, which has been reported to be 45 percent higher in Black patients when compared with other patients.[11]

Adverse events

Treatment with mTOR inhibitors can be complicated by adverse events. The most frequently occurring adverse events are stomatitis, rash, anemia, fatigue, hyperglycemia/hypertriglyceridemia, decreased appetite, nausea, and diarrhea. Additionally, interstitial lung disease is an adverse event of particular importance. mTORi-induced ILD often is asymptomatic (with ground glass abnormalities on chest CT) or mild symptomatic (with a non-productive cough), but can be very severe as well. Even fatalities have been described. Careful diagnosis and treatment, therefore, is essential. Recently, a new diagnostic and therapeutic management approach has been proposed.[22]

Use in kidney transplantation

Sirolimus and everolimus have been utilized in a number of settings in kidney transplantation, although their use has been decreasing due to the various problems outlined above.[23]

●**Maintenance therapy** – The efficacy of mTOR inhibitors for primary maintenance immunosuppressive therapy in kidney transplant recipients is well documented. However, early posttransplantation complications of sirolimus, particularly delayed allograft function, poor wound healing, adverse short-term outcomes, and an increased incidence of lymphoceles, have limited the de novo use of mTOR inhibitors at some centers.[24]

●**Glucocorticoid withdrawal** – In an attempt to minimize glucocorticoid-induced morbidity, sirolimus has been administered to kidney transplant recipients in whom glucocorticoids were eventually withdrawn. This is discussed separately.[25]

●**Chronic renal allograft nephropathy** – A discussion of the use of sirolimus in patients with chronic renal allograft nephropathy is discussed separately.[26]

●**Refractory kidney transplant rejection** – The efficacy of sirolimus for refractory renal allograft rejection has been evaluated in limited preliminary studies. Further study is required to better understand the role of sirolimus in this setting.[27]

●**Patients at risk for cytomegalovirus (CMV) infection** – A lower incidence and severity of CMV infection in transplant recipients treated with mTOR inhibitors has been observed in several clinical trials and meta-analyses. Future trials designed to test the effect of mTOR inhibitors on CMV infection should be conducted.[28]

●**Patients with skin cancer** – Sirolimus may have an antineoplastic effect among kidney transplant recipients with squamous cell carcinoma. In one trial, kidney transplant recipients with at least one cutaneous squamous cell carcinoma were randomly assigned to receive sirolimus as a substitute for calcineurin inhibitors or to maintain calcineurin inhibitor therapy. Patients who were converted to sirolimus, compared with those maintained on calcineurin inhibitors, had a lower rate of new squamous cell carcinomas (22 versus 39 percent). More adverse events occurred in the sirolimus group, resulting in discontinuation of sirolimus in 23 percent of patients.[29]

Effect of mTOR inhibitors on post-transplant renal function

From *in vitro* experimental studies it has long been recognised that the combination of a CNI and an mTOR inhibitor provide immunological synergy. However, the main limitation of this combination in clinical practice is the enhanced nephrotoxicity of the CNI. Randomised trials using everolimus with a reduced dose of CsA have nevertheless demonstrated that efficacy is maintained without any detriment to renal function, at least at the relatively early time point of 24 months. This approach has allowed a 60% reduction in exposure to the CNI over a 12-month timeframe. The longer term effect of this approach on renal function is not known and awaits further observation.[30]

Calcineurin Inhibitors for Renal Transplant

Calcineurin inhibitors

Calcineurin inhibitors are immunosuppressants used in the management of autoimmune conditions such as lupus nephritis, idiopathic inflammatory myositis, interstitial lung disease, atopic dermatitis, and many more. In addition, they are used as mainstays for immunosuppression in solid organ transplants.[31]

Cyclosporine

Tacrolimus

Pimecrolimus

Voclosporin

Mechanism of Action

Calcineurin is a complex of phosphatases composed of a 61-kDa calmodulin-binding catalytic subunit (calcineurin-A) and a 19-kDa calcium-binding regulatory subunit (calcineurin-B). This protein participates in a wide range of cellular processes and calcium-dependent signal transduction pathways, including T cell activation.[32]

Calcineurin Inhibitors for Kidney Transplant

Tacrolimus-based regimens are currently the mainstay at most kidney transplant programs in the United States. Over 85% of kidney transplant recipients are discharged from their transplant admission on tacrolimus as part of their maintenance immunosuppressive regimen. This is largely because tacrolimus is more potent and is associated with less rejection and nephrotoxicity than cyclosporine.[33]

CNI Monitoring

Selection of the appropriate timing and target values for measuring CNI drug levels is another important component of clinical care. It is recommended that tacrolimus be monitored at trough levels (usually just prior to morning dose administration) as this timepoint is thought to correlate well with concentration of the drug in circulation. However, a recent publication reported that pooled data from three large randomized controlled trials was unable to find any significant correlations between tacrolimus trough levels at five time points (day 3, 10 and 14, and months 1 and 6 post-transplant) and the incidence of biopsy proven rejection in kidney transplant recipients.[34]

CNI Management and Minimization Strategies

Table 1. Alternatives to Full Dose CNI Regimens **(Andrassy et al., 2020)**

Strategy	Definition	Timing
Minimization	Lower dosage of CNI	Planned de novo, or result of adverse event
Conversion	Tapering of CNI dose until eliminated and replaced with other immunosuppressant	Usually result of adverse event
Withdrawal	Tapering of CNI dose until eliminated; may be replaced with other immunosuppressant	Planned de novo or result of adverse event
Avoidance	No CNI given; other immunosuppressant used	Planned de novo

REFERENCES

1. Abecassis M, Bartlett ST, Collins AJ, et al. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI™) conference. *Clinical Journal of the American Society of Nephrology*. 2008;3(2):471-480.
2. Srinivas TR, Meier-Kriesche H-U. Minimizing immunosuppression, an alternative approach to reducing side effects: objectives and interim result. *Clinical Journal of the American Society of Nephrology*. 2008;3(Supplement 2):S101-S116.
3. Flechner SM. mTOR inhibition and clinical transplantation: kidney. *Transplantation*. 2018;102(2S):S17-S18.
4. Abramyan S, Hanlon M. Kidney Transplantation. 2021;
5. Shah PH, Leibovich BC. Gross and Laparoscopic Anatomy of the Upper Tract and Retroperitoneum. *Urologic Principles and Practice*. 2020:3-23.
6. Santos J, Oliveira P, Malheiro J, et al. Predicting 6-month mortality in incident elderly dialysis patients: a simple prognostic score. *Kidney and Blood Pressure Research*. 2020;45(1):38-50.
7. Al Zarouni M. Abdominal Wall Reconstruction with the Two-step Technique: Procedure Optimization and Three-year Follow-up in 26 Surgeries. *Plastic and Reconstructive Surgery Global Open*. 2019;7(5)
8. Kakaei F, Nikeghbalian S, Malekhosseini SA. Kidney transplantation techniques. *Current Issues and Future Direction in Kidney Transplantation*. 2013:3655.
9. Khadjibaev A, Khadjibaev F, Rakhimova R, et al. Three-Year Experience of Kidney Transplantation at a Single Center in Uzbekistan. *Experimental and Clinical Transplantation: Official Journal of the Middle East Society for Organ Transplantation*. 2022;20(Suppl 1):24-30.
10. Alloway RR, Woodle ES, Abramowicz D, et al. Rabbit anti-thymocyte globulin for the prevention of acute rejection in kidney transplantation. *American Journal of Transplantation*. 2019;19(8):2252-2261.
11. Hardinger K, Brennan DC. Kidney transplantation in adults: Maintenance immunosuppressive therapy. UpToDate Waltham, MA, USA; 2020.
12. Neuwirt H, Rudnicki M, Schratzberger P, Pirklbauer M, Kronbichler A, Mayer G. Immunosuppression after renal transplantation. *memo-Magazine of European Medical Oncology*. 2019;12:216-221.
13. Ong PS, Wang LZ, Dai X, Tseng SH, Loo SJ, Sethi G. Judicious toggling of mTOR activity to combat insulin resistance and cancer: current evidence and perspectives. *Frontiers in pharmacology*. 2016;7:395.
14. Thomas PG, Mohanka R. Immunosuppression in Liver Transplantation. *GI Surgery Annual: Volume 26*. Springer; 2022:185-219.
15. Press NJ, Joly E, Ertl P. Natural product drug delivery: A special challenge? *Progress in medicinal chemistry*. Elsevier; 2019:157-187.

16. Hussain Y, Khan H. Immunosuppressive Drugs. *Encyclopedia of Infection and Immunity*. 2022:726.
17. Basté Rotllan N. Potential use of multikinase inhibitors in immunosuppressed patients with malignancies including thyroid cancer. *Cancer Medicine*. 2022;11:10-16.
18. Job KM, Roberts JK, Enioutina EY, et al. Treatment optimization of maintenance immunosuppressive agents in pediatric renal transplant recipients. *Expert Opinion on Drug Metabolism & Toxicology*. 2021;17(7):747-765.
19. MacPhee IA. Immunosuppression for Renal Transplantation. *Primer on Nephrology*. Springer; 2022:1605-1625.
20. Dos Santos KC, Dos Reis LR, Rodero CF, et al. Bioproperties, Nanostructured System and Analytical and Bioanalytical Methods for Determination of Rapamycin: A Review. *Critical Reviews in Analytical Chemistry*. 2022;52(5):897-905.
21. McCune JS, Bemer MJ, Long-Boyle J. Pharmacokinetics, pharmacodynamics, and pharmacogenomics of immunosuppressants in allogeneic hematopoietic cell transplantation: part II. *Clinical pharmacokinetics*. 2016;55(5):551-593.
22. Willemsen AE, Grutters JC, Gerritsen WR, Van Erp NP, Van Herpen CM, Tol J. mTOR inhibitor- induced interstitial lung disease in cancer patients: Comprehensive review and a practical management algorithm. *International journal of cancer*. 2016;138(10):2312-2321.
23. Kirk AD, Adams AB, Durrbach A, et al. Optimization of de novo belatacept-based immunosuppression administered to renal transplant recipients. *American Journal of Transplantation*. 2021;21(5):1691-1698.
24. Ortiz AC, Petrossian G, Addonizio K, et al. Short-term decreased post transplant lymphoproliferative disorder risk after kidney transplantation using two novel regimens. *Transplant Immunology*. 2023;76:101774.
25. Dowd M, Shary N, Wang M, Colegio OR. Direct Dermatologic Side Effects of Immunosuppressive Therapy in Solid Organ Transplant Recipients. *Dermatology and Solid Organ Transplantation*. CRC Press; 2021:247-260.
26. Sanders J-SF, Bemelman FJ, Messchendorp AL, et al. The RECOVAC immune-response study: the immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. *Transplantation*. 2022;106(4):821.
27. Morris BA, Alfson A, Davies G, Kaufman D, Bradley KA. Local Graft Irradiation for Acute, Medication Refractory Transplant Rejection of a Pancreas Alone Graft: A Case Report. *Advances in Radiation Oncology*. 2023;8(2):101168.
28. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical transplantation*. 2019;33(9):e13512.
29. Ying T, Wong G, Lim W, et al. De novo or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: A trial-based linkage study. *American Journal of Transplantation*. 2018;18(12):2977-2986.
30. Franzin R, Netti GS, Spadaccino F, et al. The use of immune checkpoint inhibitors in oncology and the occurrence of AKI: where do we stand? *Frontiers in Immunology*. 2020;11:574271.
31. Ujiie H, Rosmarin D, Schön MP, et al. Unmet medical needs in chronic, non-communicable inflammatory skin diseases. *Frontiers in Medicine*. 2022;9
32. Ponticelli C, Reggiani F, Moroni G. Old and new calcineurin inhibitors in lupus nephritis. *Journal of Clinical Medicine*. 2021;10(21):4832.
33. Pilch NA, Bowman LJ, Taber DJ. Immunosuppression trends in solid organ transplantation: the future of individualization, monitoring, and management. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2021;41(1):119-131.
34. Green H, Rahamimov R, Spectre G, et al. Apixaban level and its influence on immunosuppression and graft outcome in kidney transplant recipients with atrial fibrillation. *Therapeutic Drug Monitoring*. 2021;43(5):637-644.