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Review article
Pregledni članak

CURRENT BIOCHEMICAL MONITORING AND RISK MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY AFTER TRANSPLANTATION

SAVREMENI BIOHEMIJSKI MONITORING I UPRAVLJANJE RIZIKOM IMUNOSUPRESIVNOG TRETMANA NAKON TRANSPLANTACIJE

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Summary

Immunosuppressive drugs play a crucial role in the inhibition of immune reaction and prevention of graft rejection as well as in the pharmacotherapy of autoimmune disorders. Effective immunosuppression should provide an adequate safety profile and improve treatment outcomes and the patients' quality of life. High-risk transplant recipients may be identified, but a definitive prediction model has still not been recognized. Therapeutic drug monitoring (TDM) for immunosuppressive drugs is an essential, but at the same time insufficient tool due to low predictability of drug exposition and marked pharmacokinetic variability. Parallel therapeutic, biochemical and clinical monitoring may successfully optimize and individualize therapy for transplanted recipients, providing optimal medical outcomes. Modern pharmacotherapy management should include new biomarkers with better sensitivity and specificity that can identify early cell damage. The aim of this study was to point out the importance of finding new biomarkers that would enable early detection of adverse drug events and cell damage in organ transplant recipients. We wanted to confirm the importance of routine biochemical monitoring in improving the safety of immunosuppressive treatment.

Keywords: biochemical monitoring, biomarkers, organ transplantation, risk management

Kratak sadržaj

Imunosupresivni protokol ima značajnu ulogu u inhibiciji imunog odgovora prilikom transplantacije organa, kao i u farmakoterapiji autoimunih bolesti. Efektivna imunosupresija mora posedovati odgovarajući bezbednosni profil i obezbediti pozitivne terapijske odgovore i bolji kvalitet života pacijenta. Do sada nije definisan model koji predviđa rizik za pacijente sa transplantiranim organom, iako su prepoznati najznačajniji faktori rizika. Terapijski monitoring imunosupresivnih lekova (TDM) osnovno je, ali ne i dovoljno sredstvo za predviđanje ukupne izloženosti organizma lekovima sa varijabilnom kinetikom. Istovremeni terapijski, biohemijski i klinički monitoring mogu uspešno prilagoditi terapiju individualnom pacijentu sa optimalnim medicinskim odgovorima. Savremeno upravljanje terapijom trebalo bi da uključi nove biomarkere, čija senzitivnost i specifičnost omogućavaju identifikaciju ranog ćelijskog oštećenja. Cilj ovog rada je da istakne važnost pronalaženja novih biomarkera koji bi imali mogućnost rane detekcije neželjenih efekata lekova i ćelijskog oštećenja kod pacijenata sa transplantiranim organom. Pored toga, razmatran je značaj rutinskog biohemijskog monitoringa u svrhu poboljšanja bezbednosti imunosupresivnog protokola.

Ključne reči: biohemijski monitoring, biomarkeri, transplantacija organa, upravljanje rizikom

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Introduction

Immunosuppressive drugs play a crucial role in the inhibition of immune reaction and prevention of graft rejection as well as in the pharmacotherapy of autoimmune disorders. Immunosuppression undergoes four stages in patients with transplanted organs: desensitization, induction of immunosuppression, maintenance therapy and treatment of graft rejection episodes (1). Effective immunosuppression must provide an adequate safety profile and favorable treatment outcomes. In everyday clinical practice, however, a relatively high proportion of patients on immunosuppressive treatment may experience under-immunosuppression or over-immunosuppression (2, 3). Nowadays, a tertiary or quaternary protocol has a better risk benefit ratio due to lower individual doses of each immunosuppressant. The most commonly used immunosuppressive drugs are: antimetabolites (azathioprine, mycophenolate mofetil – MMF), calcineurin inhibitors – CNI (tacrolimus – Tac, cyclosporine A – CyA), inhibitors of mammalian target of rapamycin – mTOR (sirolimus, everolimus) and monoclonal antibodies. Also, corticosteroids are an important part of an immunosuppression protocol. The SYMPHONY study suggested better safety and efficacy treatment profiles of low-dose immunosuppressive regimens compared with standard-dose regimens in renal transplant recipients (4).

High-risk transplant recipients can be identified, but no definitive prediction model exists. In order to minimize the side and toxic effects of immunosuppressants in setting a drug regimen, the following should be considered:

- indication
- associated disease
- the characteristics of the patient
- the pharmacokinetic profile of the drug
- co-administered immunosuppressive therapy
- other drugs and dietary or herbal products in therapy.

Simultaneous risk management, which includes development of risk models and constant evaluation of therapeutic regimens, leads to better clinical effectiveness and cost-effectiveness of pharmacotherapy and better patients' quality of life (5). A low therapeutic index, high potential for drug–drug interactions, severe toxicity, and pharmacokinetic variability of the immunosuppressive drugs may justify the implementation of risk management in order to improve the efficacy and safety of immunosuppression and therefore patient and graft long-term survival (6, 7).

Therapeutic drug monitoring (TDM) for immunosuppressive drugs is an essential, but at the same time insufficient tool due to low predictability of drug exposition and marked pharmacokinetic variability caused by different factors, including genetic polymorphism of metabolizing enzymes and drug transporters. Hence, parallel therapeutic, biochemical and clinical monitoring may successfully optimize and individualize therapy for transplanted recipients providing optimal medical outcomes (8, 9).

Monitoring of selected biochemical biomarkers may indicate early organ damage, adverse effects of immunosuppressive treatment and/or organ rejection. Therefore, it may provide adequate evaluation of the therapy safety profile (10). The standard biochemical markers of organ injury are an important part of the biochemical monitoring of transplanted patients, but there is a constant tendency to find new, specific markers that would indicate changes in subcellular structures and help prevent problems (11, 12). The aim of this study was to point out the importance of finding new biomarkers that would enable early detection of adverse drug events and cell damage within organ transplant recipients. Moreover, we wanted to confirm the importance of routine biochemical monitoring in improving the safety of immunosuppressive treatment.

Immunosuppressive protocol in organ transplantation

The advancing science of immunosuppression and novel drugs have led to more transplants, longer graft survival and better quality of life for transplanted patients. Furthermore, a priority in the long-term immunosuppressive therapy is to give opportunity for graft survival, but also for reduction of side effects and proper evaluation of efficacy and safety regimens (4).

An immunosuppressive regimen is always a combination of several immunosuppressive drugs chosen in relation to the type of disease, intervention, characteristics of drugs and patient. Development of opportunistic microbial infections and a spectrum of unique cancers, many of which are caused by oncogenic viruses, represent important adverse events in immunosuppressive therapy (7).

Frequent side and toxic effects of the most commonly used immunosuppressive drugs are given in *Table I*. Tertiary or quaternary immunosuppressive protocols showed a better risk benefit ratio compared with only one drug treatment. For example, numerous studies have confirmed the protective influence of mycophenolate mofetil against the toxic effects on kidneys, liver and heart induced by tacrolimus (13, 14).

Regular monitoring of standard biochemical parameters in patients under an immunosuppressive protocol might help in immunosuppressive dose adjustments and evaluation of adverse effects of immunosuppressive therapy, which confirms a previous investigation conducted among kidney transplant recipients in the early post-transplantation period (15, 16).

Table I An overview of the side effects and toxicity potential of immunosuppressive drugs.

Immunosuppressive drugs	Side effects	Toxicity
Tacrolimus	hypertension, neurological side effects (tremor, headache, neuralgia, peripheral neuropathy)	nephrotoxicity, hepatotoxicity, cardiotoxicity, neurotoxicity
Cyclosporine A	hypertension, hyperlipidemia, neurological side effects (tremor, headache, neuralgia, peripheral neuropathy), hirsutism, gingivitis, gum hyperplasia, hypomagnesemia	nephrotoxicity, hepatotoxicity, cardiotoxicity, neurotoxicity
Mycophenolate mofetil/mycophenolic acid	gastrointestinal side effects (abdominal pain, nausea, diarrhea) and hematological side effects (anemia, leukopenia)	embrio-fetal toxicity, neurotoxicity
Sirolimus	hernia, hyperlipidemia, edema, anemia, proteinuria, thrombotic microangiopathy, thrombosis, pneumonitis	nephrotoxicity
Corticosteroids	susceptibility to infection, impaired wound healing, growth suppression in children, osteoporosis, aseptic necrosis of bone, cataracts, glucose intolerance, hypertension, emotional liability, insomnia, manic and depressive psychosis, gastric ulcers, hyperlipidemia, polyphagia, obesity, acne	hepatotoxicity
Monoclonal Antibodies	infections, malignancies, hematological complications (leukopenia and thrombocytopenia), flu-like symptoms, hypotension, tachycardia, pyrexia, chills/rigors, nausea, urticaria, dyspnea, rash, emesis, bronchospasm	

Finding the ideal therapeutic regimen for immunosuppressive drugs is the result of knowledge of existing biomarkers, their sensitivity, and the possibilities of newly discovered biomarkers. During the biochemical monitoring of patients on immunosuppressive therapy, three types of biomarkers are discussed: those associated with the risk of rejection (alloreactivity/tolerance) and those reflecting individual response to an immunosuppressive protocol (2, 7, 17). Modern risk management of immunosuppressive therapy includes the pharmacokinetic and pharmacoeconomic approach, with biomarkers as an important prediction factor. Identification of novel biomarkers with more sensitivity and specificity and their integration in a mathematic model is a way to an optimal clinical outcome (18).

Biomarkers after organ transplantation and risk management

Renal function can be estimated by standard biochemical parameters including serum levels of creatinine, urea, potassium, sodium, calcium, as well as urine levels of albumin, α_1- and β_2-microglobulin. They may confirm the existence of kidney damage, but do not reveal the mechanisms and places of damage with sufficient precision. This is an indication for the investigation of more specific early cell damage biomarkers, which could lead to an adequate medical reaction (19). The first disadvantage of serum creatinine is the fact that its serum concentration depends on age, gender, muscle mass, muscle metabolism, co-administered drugs and hydration status. Also, serum creatinine concentrations may not change until a significant amount of kidney function has already been lost. Moreover, only a few days post-transplantation, when steady state equilibrium has been reached, serum creatinine concentration shows the accurate status of the kidney function (20). Co-medication drugs may also influence serum creatinine concentration or the analytic procedure, which is shown in *Table II*.

Risk management of organ transplant recipients requires the use of the early biomarkers of acute or chronic kidney and liver injury as well. This may provide a better prognosis for clinical outcomes and improve the quality of life with decreasing medical costs (21, 22).

Recent studies have aimed to relate biomarkers to the indications which will be of particular benefit for timely information on the precise location of damage.

Table II Influence of drugs on serum creatinine level.

	Mechanism		
	Decreased creatinine secretion	Increased creatinine production	Interference with assays
Causes	Trimethoprim Ranitidine	Finofibrates Rhabdomyolysis Meat intake	Flucytosine Acetoacetate Cefoxitin

The markers might be found below: cystatin C (CysC), neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule (KIM-1), urinary N-acetylglucosaminidase (NAG), fatty acid binding protein L (L-FABP), Micro RNAs (miRNAs). The explanation of the mechanisms of the renal function impairment on the subcellular level after transplantation, led to numerous potential nephrotoxicity biomarkers. Interleukin (IL) 18, as well as IL6 and IL8 are some of the new high-sensitivity markers of tubular damage and might represent an improvement of diagnosis and prognosis for the patient.

Previous investigation showed that the increase in the level of CysC occurs while other parameters of renal function are still at a normal level (23). It should be noted that structural damage to the kidneys may exist and be detected independently of reversible functional damage, but both require early diagnosis and intervention or otherwise may cause irreversible damage. The use of CysC in routine clinical practice provides better understanding and interpretation of the nature of existing damage and helps the risk management plan (23, 24).

Andersen et al. (25) suggest using CysC as a more sensitive marker of renal function compared to plasma creatinine – especially in situations in which there is only a moderate decrease in glomerular filtration rate (GFR). In the »creatinine blind area« CysC may have advantage in the diagnostics of initial renal impairment. Especially after renal transplantation, CysC enzymatic measurements can detect early GFR impairment after renal transplantation in adults. Research of Astenazi et al. focused on CysC, NGAL, osteopontin, clusterin, and α-glutathione S-transferase and aimed to determine whether these biomarkers can predict important clinical outcomes (26). Wei et al. (24) also showed that serum and urine levels of CysC are sensitive markers of renal function. The level of CysC as a kidney damage marker should be considered by taking into account factors such as the characteristics of patients and analytic assays as well as the plasma level of bilirubin. The increase in serum bilirubin and CysC at the same time indicates liver damage.

Neutrophil gelatinase associated lipocalin is a protein of the lipocalin family, which grows through neutrophils and other epithelial cells (including aggregation proximal tubules chains). As a new and a very sensitive, specific and promising biomarker of renal function, NGAL appeared in 2008 (27). Previous studies indicate that the NGAL monitoring is an important predictor of renal dysfunction, providing an opportunity for much earlier reaction in different acute kidney injuries and a variety of clinical situations of chronic kidney dysfunction (28–30). Further larger cohorts, which would include multiple clinical situations, may validate the sensitivity and specificity of NGAL concentration measurements as well as the pharmacoeconomics of its introduction in routine clinical practice. There are numerous studies which show that the measurement of serum NGAL level with considerable specificity and full sensitivity makes it possible to predict the incidence of acute renal failure after a renal graft. For this reason, this biomarker can be used in the clinical examinations of transplanted patients (28).

Previous studies also showed that the monitoring of NAG urine activity is useful in the evaluation of early proximal tubule damage (31) and in predicting the long-term function of the transplanted kidneys recipients (32, 33).

After liver transplantation, it is necessary to secure stable graft function as well as identification of early cell damage by immunosuppressive drugs in the immunosuppressed patients. Drugs can directly damage the hepatocyte in a dose-dependent predictable manner or by idiosyncrasy or during metabolic activation (34). Structural hepatocyte damage and tissue necrosis, formation of the antigen complex, as well as toxic effects of drugs might be the cause of changes in the value of biochemical parameters representing the liver function status. The standard diagnostic procedure is a combination of clinical observation, reading of the value of activity of transaminases, INR extension, increased levels of gamma GT, LDH and bilirubin as routine biochemical parameters, and often liver biopsy.

Clark et al. (11) suggested that promising biomarkers may provide information on the hepatic specificity of an injury like micro RNA-122 or keratin-18 for mechanistic liver insight. However, these biomarkers have not been formally qualified and are not in routine clinical use yet (35). Risk management is crucial for graft survival, as well as the patients' quality of life, because the exclusion of a drug from therapy in immunosuppressed patients due to liver damage is not often the best choice. Pharmacoeconomics of immunosuppressive therapy involves a series of decisions which ensure better health outcomes for the patient.

Biochemical monitoring of liver function points to miRNAs as biomarkers of higher sensitivity than the existing routine markers such as alanine aminotransferase (ALT) and troponins (36). The development of

Table III Biomarkers of neural damage.

Protein based Biomarker	Endpoint
GFAP (glial fibrillary acidic protein)	Biomarker of all types of neural (neuronal and glial) damage
MAP-2 (microtubule-associated protein)	Biomarker of dendritic injury
F2-IsoPs (F2-iso prostanes)	Indirect measurement of oxidative injury
MBP (myelin basic protein)	Biomarker of myelin disruption
Neurofilament (light chain and phosphorylated heavy chain)	Biomarkers of axonal injury

miRNA based diagnostic might influence the diagnosis and medical activity in patients on immunosuppressive therapy. MicroRNAs (miRNAs), as a group of new biomarkers, are short single-stranded RNA non-coding sequences that have a role in the post-transcriptional regulation of genes. One of the most clearly established roles for miRNAs is their contribution to organism development and cell differentiation, which makes miRNAs an indicator for cell damage detection. Nowadays, miRNA profiling is incorporated into the process of drug safety testing, first of all in hepatotoxicity and cardiotoxicity testing (37). Due to their tissue specificity, miRNAs show rapid and tissue-specific change in body fluids induced by cell injury. In addition, while circulating miRNAs are stable, the level of extracellular miRNAs differs between healthy and diseased individuals (38). The confirmation of miRNA biomarkers requires validation of the miRNA specific tissue expression profiles and determination of specific miRNA expression following cellular damage. They are investigated as markers of diagnosis and prognosis of drug induced kidney injury (39, 40).

Diagnostics of neuronal damage is achieved by using a combination of data derived from functional tests, electrophysiological measurements and histopathologic analysis of tissue. Neurotoxicity has been linked to a number of common drugs, but efficient and accurate methods to detect neuronal damage are still lacking. There are two groups of neurological damage biomarkers: fluid-based and protein-based. Biomarkers that are measurable with minimally invasive techniques, such as biological fluid-based markers (found in serum, plasma, urine and cerebrospinal fluid) could provide the opportunity for better diagnostic and treatment assessments (41). A few biomarkers associated with nervous tissue damage have been validated for routine use in clinical practice, but they fail to demonstrate predictive clinical value. Additionally, because the gene expression in neural cells is modified when cells are damaged, biofluids represent an opportunity for identifying alterations in cellular RNA. Some of the promising neurotoxicity biomarkers are listed in *Table III*. These biomarkers indicate specific types of neural damage associated with neurotoxicity (41).

Conclusion

Modern immunosuppressive protocols should offer higher graft survival rates and better patients' quality of life with medical costs minimization. Therapeutic drug monitoring is the basis of rational pharmacotherapy in transplant recipients. Still, TDM is an insufficient tool for achieving optimal treatment outcomes due to genetic polymorphisms and drug pharmacokinetic variability. This may lead to unexpected clinical responses. Generally, regular biochemical monitoring could provide information regarding graft and patient status, which can be essential in the risk management. Early diagnosis of rejection episodes or toxic effects of particular immunosuppressives gives the opportunity of adequate response. Early medical response means better clinical outcomes and decreased treatment costs. Finding new biomarkers with better sensitivity and specificity which could indicate changes at the level of cellular damage and their introduction in clinical practice may be justified through better cost/benefit and cost/effectiveness ratios. Therefore, research that may lead to the introduction of novel biomarkers in routine practice under particular circumstances is of utmost importance.

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Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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