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# Current methods of the analysis of immunosuppressive agents in clinical materials: A review

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ABSTRACT

More than 100 000 solid organ transplantations are performed every year worldwide. Calcineurin (cyclosporine A, tacrolimus), serine/threonine kinase (sirolimus, everolimus) and inosine monophosphate dehydrogenase inhibitor (mycophenolate mofetil), are the most common drugs used as immunosuppressive agents after solid organ transplantation. Immunosuppressive therapy, although necessary after transplantation, is associated with many adverse consequences, including the formation of secondary metabolites of drugs and the induction of their side effects. Calcineurin inhibitors are associated with nephrotoxicity, cardiotoxicity and neurotoxicity; moreover, they increase the risk of many diseases after transplantation. The review presents a study of the movement of drugs in the body, including the processes of absorption, distribution, localisation in tissues, biotransformation and excretion, and also their accompanying side effects. Therefore, there is a necessity to monitor immunosuppressants, especially because these drugs are characterised by narrow therapeutic ranges. Their incorrect concentrations in a patient's blood could result in transplant rejection or in the accumulation of toxic effects. Immunosuppressive pharmaceuticals are macrolide lactones, peptides, and high molecular weight molecules that can be metabolised to several metabolites. Therefore the two main analytical methods used for their determination are high performance liquid chromatography with various detection methods and immunoassay methods. Despite the rapid development of new analytical methods of analysing immunosuppressive agents, the application of the latest generation of detectors and increasing sensitivity of such methods, there is still a great demand for the development of highly selective, sensitive, specific, rapid and relatively simple methods of immunosuppressive drugs analysis.

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## 1. Introduction/short history of used ISDs

The immune system detects and eliminates tumor cells and foreign pathogens, simultaneously avoiding self-recognition. If the mechanisms of the immune response are over-reactive it can lead to autoimmunity. However, the immune response is responsible not only for autoimmune diseases or allergic reactions, but also contributes to the rejection of organs after transplantation. About 5% of the population in developed countries develops an autoimmune disease during life, and these numbers are still increasing [1]. More than 100 000 solid organ transplantations are performed every year worldwide [2]. The most frequently used immunosuppressive drugs (ISDs) to prevent the rejection of transplanted organs are cyclosporine A (CsA), tacrolimus (FK-506), sirolimus (SIR) everolimus (EvE), and a semisynthetic derivative of mycophenolic acid—mycophenolate mofetil (MMF) (Fig. 1) [3]. Currently, after transplantation, patients generally receive CsA or FK-506, and MMF, as well as prednisolone or methylprednisolone [4]. Some of these ISDs are also used for the treatment of autoimmune diseases [1,5].

Immunosuppressive therapy in the 1960s and 1970s was based mainly on azathioprine (AZA) and steroids [6]. In the late 70s for the first time a CsA was used after a bone marrow transplantation in an experimental animal model [7]. In the early 1980s triple therapy (CsA, AZA and glucocorticoid) was introduced in clinical trials after transplantation [8]. The result was a more effective treatment and increase in 1- and 5-year survival rates to 32.9% and 20.0%, respectively, when using AZA, and 69.7% and 62.8%, respectively, for CsA treatment [6]. AZA was the first cytostatic agent used after transplantation [9]. Currently, it is used only in the treatment of autoimmune aggression disease [10]. The reason is the development of neoplasia, which was detected in transplant patients treated by AZA [9]. An increased risk of squamous cell carcinoma and Hodgkin's lymphoma [11] are confirmed side effects

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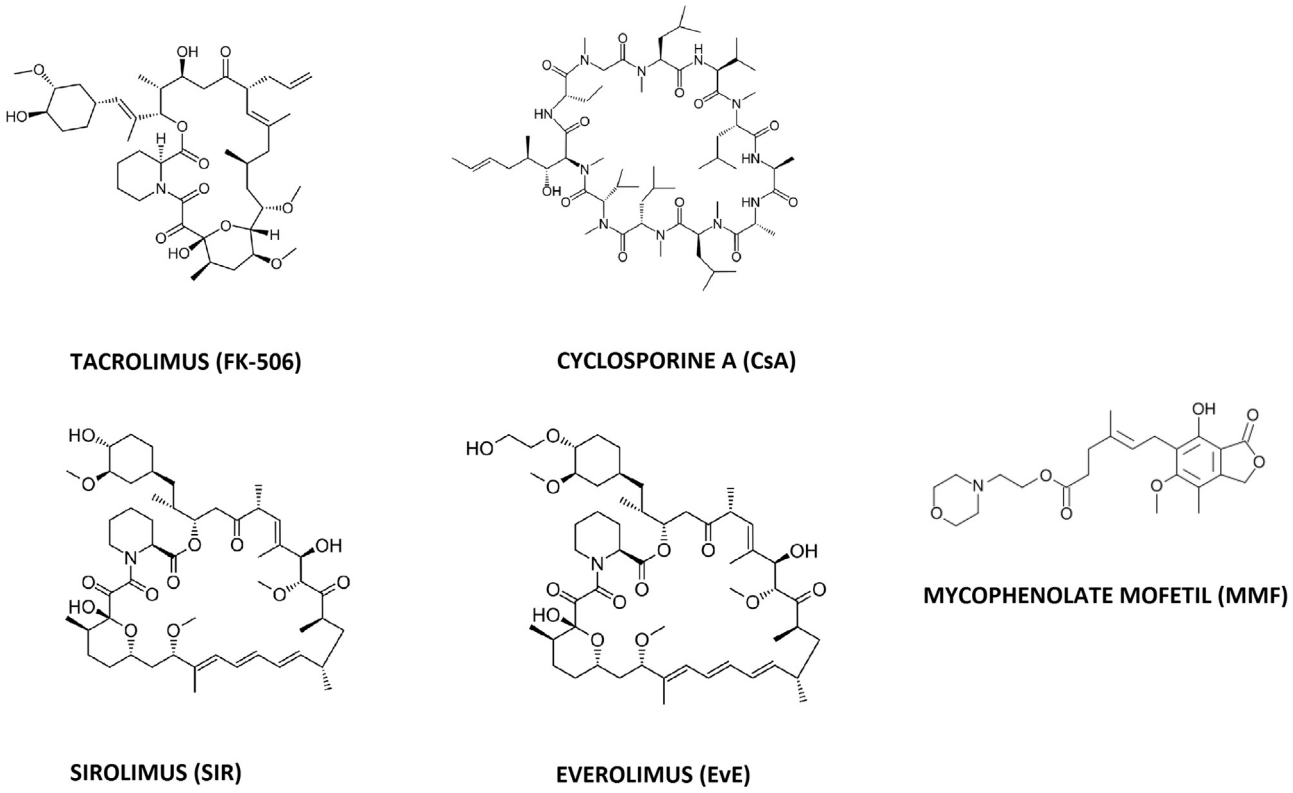


**Fig. 1.** Chemical structures of selected immunosuppressive drugs.

of AZA. What is the cause? According to Speck and Rosenkranz [9] this may be caused by anaerobic conditions in an organism. Finally, AZA turned out to be a very toxic drug with many very adverse effects. The toxicity of azathioprine is manifested by teratogenesis, infection, hepatotoxicity, neoplasia [12] and anemia, thrombocytopenia, leukopenia, and hypersensitivity reactions [11]. What is very important is that immunosuppressants are very rarely a cause of marrow failure [13], whereas after the AZA treatment a posttransplant lymphoproliferative disorder (PTLD) was described [14,15]. The replacement of AZA with MMF in triple therapy with CsA and corticosteroids turned out to be more efficacious [16]. Moreover, the application of a combination of SIR with CsA or FK-506 is a more effective therapy than the use of these drugs separately [17]. It is also the next step for a reduction of the concentration of used drugs [18].

## 2. Pharmaceutical preparations/characterisation of pharmaceuticals

### 2.1. Pharmacokinetics

In this review the most commonly used ISDs were described, characterised by a narrow therapeutic window. Therefore, these pharmaceuticals require therapeutic drug monitoring—the measurement of their quantification, the determination of their metabolites and the interaction/impact of co-medicated drugs

### 2.2. Tacrolimus—FK-506

FK-506 is macrocyclic lactone isolated from *Streptomyces tsukubaensis* [19]. Together with CsA, FK-506 is the most popular ISD used following organ transplantation. FK-506 was originally used after liver transplants; however, currently, it is used in the management of heart, lung, kidney, pancreas, small bowel and bone marrow transplants [20]. FK-506 is not only an ISD, it is also used as an agent for treating autoimmune [5] and renal, endocrine, neurologic or eye disease [21].

The FK-506 molecule binds with FKBP12 – the isoform of cytoplasmic immunophilins FKPB [22] – and creates the calcineurin inhibitory complex [serine-threonine protein phosphatase] [23]. Calcium-dependent signal transduction is disturbed and the following step is the inactivation of transcription factors [24,25]. As a consequence, FK-506 decreases T-lymphocyte activation and downregulates the expression of inflammatory response-related genes [24,25]. FK-506 has a higher affinity for FKPB than CsA—FK-506 inhibits also the production, proliferation and activation of T and B cells, therefore its inhibition of lymphocyte activation is 10–100 times stronger than CsA [26].

FK-506 is characterised by small bioavailability after oral administration [about 14%], therefore it is administered intravenously, immediately after an operation and oral doses need to be higher than i.v. doses [27]. According to some authors, its bioavailability is about 25% but ranges from 5% to 93% [28,29] and from 10% to 60% [23]. FK-506 has a high affinity for albumin, lymphocytes and erythrocytes, which protects it against premature metabolism by hepatic enzymes and promotes slow drug release [19].

FK-506 is eliminated through the liver and the intestinal cytochrome P450 (CYP) 3A subfamily (Fig. 2) [5,12,23]. Oxidised metabolites are excreted after a comprehensive metabolism [5]. Among FK-506 metabolites there are three O-demethylated metabolites with one methoxy group at the 13-, 31- and 15-position (M-I; M-II; M-III), one mono-hydroxylated metabolite (M-IV) with OH group at the 12-position and three di-demethylated metabolites with two methoxy groups at the 15- and 31-, 13- and 31-, and 13- and 15 position [M-V; M-VI; M-VII] [30,31]. Less than 1% of FK-506 is excreted unchanged in urine [32,33] (according to Rahman et al. [19] and Iwasaki [5]—less than 0,5% by the urine or faeces after oral and i.v. administration) but 95% of FK-506 metabo-

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