

# Importance of Therapeutic Drug Monitoring of Immunosuppressant Drugs Using Cost-Effective Analytical Methods

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Immunosuppressant drugs suppress or reduce the function of the immune system by inhibiting the factors involved in the immune process.<sup>1</sup> For more than half a century, immunosuppression has been associated as an essential strategy in the treatment of autoimmune diseases, the prevention of organ transplantation rejection, and the improvement of graft survival rate.<sup>2-4</sup>

Early immunosuppressants are nonspecific and broadly disrupt the immunogenicity process which may cause several adverse effects and serious toxicities. While the new agents act more specifically and are particularly targeted to one of the immune system elements.<sup>5</sup> Nevertheless, even new immunosuppressants are not without toxic and adverse effects. In addition, most immunosuppressant drugs have a narrow therapeutic index (TI) that can lead to ineffectiveness of treatment in sub-therapeutic levels and toxicity, drug-drug, and drug-nutrient interactions in above therapeutic concentrations.<sup>3,5,6</sup>

Immunological interventions can lead to many undesired consequences and complications especially in long-term use, the most important complications are infections, malignancies, and renal dysfunction. Besides, some of the immunosuppressants, mainly after oral consumption, show inter-individual variabilities in plasma concentrations depending on patients' age, gender, diet, body weight, disease status, etc. Even the variability of drug concentration increases by immunosuppressant-induced renal failure.<sup>5,6</sup> So, therapeutic drug monitoring (TDM) for immunosuppressants is an essential necessity considered to ensure drug concentration in the bloodstream and at its action site maintain within a predefined therapeutic concentration by quantifying and continuous monitoring while reducing the likelihood of complications.<sup>7,8</sup>

Normally, after 6-12 months of transplantation, the maintenance phase of treatment begins in which the patient starts to receive oral multi-immunosuppressive medications for years. Besides the cost of organ transplantation and the induction phase, long-term use of these multidrug regimes in the maintenance phase cannot

be cost-effective for the patient.<sup>9</sup> On average the cost of immunosuppressants is between \$10 000 to \$14 000 every year. The inefficiency of the treatment and adverse effects such as renal failure can multiply this cost. As mentioned before to reduce the risk of infection, antibacterial and antifungal agents are prescribed in this period which may cause drug-drug interactions and subsequently increase therapeutic costs. Many studies showed a significant relationship between transplant success and the annual income of the patients.<sup>9,10</sup> Therefore, TDM of the immunosuppressants can be helpful for reducing the costs by determining the concentration of the drug and decreasing the risk of the side effects and interactions. Some points dealing with the cost reduction of analytical methods have been discussed in the literature.<sup>11</sup>

Most of the reported analytical methods for the detection of immunosuppressants in biological samples include separation-based techniques and immunoassay methods. Among chromatographic techniques, high-performance liquid chromatography (HPLC) has been reported mostly which provides high sensitivity and specificity towards the analyses. However, it is an inappropriate method for continuous monitoring due to its time-consuming process and the need for specific high-cost instruments and a skilled operator. Usually, to enhance the sensitivity, mass spectrometry is coupled to HPLC which is a high cost and sophisticated apparatus which is not suitable for on-site detection.<sup>12</sup> Immunoassay systems suffer from limitations such as high cost, lack of stability, and cross-reactivity of the used antibodies. All these methods are time-consuming for patients which need to spend time in clinical centers. For instance, in a post-renal-transplantation situation, TDM of immunosuppressants is required weekly and then tapered to every three months.<sup>12</sup> The cost of one-time analysis with new and advanced mass spectrometry methods is estimated at about \$200 000 which is increased by additional required costs (reagents and service) and \$5000–20 000 for initial equipment of immunoassay analysis plus other recurring costs (\$300–1000 per month

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depending on the extent of usage).<sup>13</sup>

In order to continually monitoring of immunosuppressants, we need analytical methods which can detect and quantify the drug concentrations with facile processes in a short period of time such as optical and electrochemical approaches. So, the development of the facile, rapid, sensitive, and selective method to use as an in-site detection platform presents a number of challenges for future investigations.<sup>14,15</sup>

Due to the fact that there is no fluorophore or chromophore in the structures of some immunosuppressive drugs, they cannot detect directly by optical methods. To overcome this problem, Jahed et al suggested an optical probe based on dopamine-capped silver nanoparticles (AgNPs) for cyclosporine detection. Each dopamine particle has two OH groups to interact with cyclosporine, the binding of which will lead to aggregation of AgNPs, and subsequently, the color of the solution changes from yellow to red. This sensor in addition to being validated for plasma samples and drug formulation is applied to measure plasma concentration of cyclosporine in two patients following oral consumption.<sup>12</sup> Mohammad Almahri et al used spectrofluorometric and chemiluminescence methods for the determination of azathioprine in a pharmaceutical formulation.<sup>16</sup> In another study, Prashanth *et al.* developed an electrochemical sensor for mycophenolate mofetil (MMF) detection using graphene oxide reduction. This sensor was applied for the determination of MMF in bulk samples and pharmaceutical formulations.<sup>17</sup> Rezaei et al reported a sensitive electrochemical method for the determination of azathioprine based on poly (vinyl alcohol)/chitosan nanofibers and silver nanoparticles.<sup>15</sup> Zhang et al designed polystyrene-gold nanorods @L-cysteine/MoS<sub>2</sub> immunosensor for electrochemical detection of tacrolimus in serum samples.<sup>18</sup> These studies provide a forward-looking perspective for future investigations of the facile and rapid sensing platforms to be used in on-site detection methods.

In conclusion, the development of a new analytical method to determine immunosuppressants is of great importance. Methods with a simple approach and reliable results are highly recommended to determine drug levels by the patient itself or health professionals using a point-of-care device and without needing any sophisticated procedures and results in interpretation time. In this regard, new advanced materials offer exceptional opportunities to develop a sensitive and specific platform for real-time monitoring of the drugs. It is obvious that the cost of analysis is a limiting parameter and its reduction is an important and critical issue in developing such a simple and accurate method.

#### Authors' Contribution

EZB: writing original draft; MEG: Conceptualization; Reviewing; TAS: Approval of the manuscript

#### Conflict of Interest

The authors have no conflicts of interest to declare.

#### Ethical Issues

Not applicable.

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