Implementation and Development of Solid Organ Transplant Pharmacotherapy in Iran

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Clinical transplant pharmacy services started half a century ago by Mitchell JF (1). Since then and especially during the last 15 years, the responsibilities of clinical transplant pharmacists have undergone a considerable evolution and expanded from inpatient setting to ambulatory care and from adults to pediatrics transplantation (2, 3).

The position of solid organ transplant (SOT) pharmacists in the multidisciplinary SOT teams has been vindicated by United Network of Organ Sharing (UNOS) bylaws and Centers for Medicare and Medicaid Services (CMS) accreditation standards for transplant centers (2). In 2004, UNOS bylaws mandated that all SOT programs should recognize pharmacist as a responsible for providing pharmaceutical care to SOT patients (2).

In 2011, the American Society of Transplantation Transplant Pharmacy Community Practice and American College of Clinical Pharmacy Immunology/ Transplantation Practice and Research Network provided guides for training and qualifications of pharmacists working in transplant patient care and detailed the involvements of pharmacists serving transplant centers (4).

In Iran, SOT pharmacotherapy service was started from April 2006 at Imam Khomeini Hospital Complex (IKHC) affiliated to Tehran University of Medical Sciences, Tehran, Iran. An academic clinical pharmacist was assigned to the kidney, liver, heart, and lung transplantation teams of this hospital. Using international transplant societies' guidelines, SOT pharmacotherapy was initiated and implemented in Iran with attempt to cover all educational, clinical and research duties in pre, peri- and post-transplantation phases. Clinical pharmacy residents attend as 1-month clinical rotation in transplant wards of IKHC for education, providing clinical pharmacy services and advancing their clinical skills under the supervision of faculty SOT pharmacotherapy specialist. Undergraduate students of pharmacy also have the opportunity to select SOT rotation as one of three clinical rotations they spend during clinical internship course.

Pre-transplantation phase

The clinical transplant pharmacist participates in weekly IKHC multidisciplinary commission for eligibility assessment of transplant candidates. In this commission the SOT pharmacist focuses on drug-related problems of the patients to make plans for managing them. Furthermore, the pharmacist assesses patients' adherence to their current medical therapy as a sign of adherence to immunosuppressive and other required drugs after transplantation and makes pharmacotherapeutic and educational measures to improve patients' medication adherence.

Peri-transplantation phase

Most of the clinical activities of the clinical SOT pharmacist and the assigned clinical pharmacy residents have been focused on transplant recipients during transplant index hospitalization and subsequent patients' hospitalizations due to post transplant complications. During daily rounds and also through written consultation forms, they provide different pharmaceutical care to SOT patients and health-care team including immunosuppressive therapeutic drug monitoring (TDM), drug dose modification based on the level of kidney and liver functions of the patients, dosing of drugs based on the body weight especially in obese or frail persons, prediction and management of adverse drug reactions (ADRs) and prediction and management of drug interactions with other drugs, supplements, food, herbal agents, or laboratory tests. In addition to pharmaceutical care services, their clinical

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research activities have improved medication therapy of Iranian transplant recipients. These researches have been published in peer-reviewed journals. Below, some of their activities are reviewed briefly.

Replacing cyclosporine by tacrolimus in immunosuppressive protocols of Iranian kidney and liver transplant recipients was started about 13 years ago in IKHC with the assistance of clinical SOT pharmacist. This change in maintenance immunosuppressive therapy after several years of experience and getting into the habit of using cyclosporine required effort for implementation among different physicians. With cooperation of SOT pharmacist, tacrolimus TDM was started with application of tacrolimus-based immunosuppressive protocols. Tacrolimus TDM showed that tacrolimus dosing using international drug databases resulted in high tacrolimus trough blood concentrations in Iranian kidney transplant recipients. Therefore, pharmacokinetic (5) and pharmacogenetic studies (6) on tacrolimus among Iranian patients were performed to find suitable starting doses of tacrolimus for Iranian transplant recipients. With the beginning of tacrolimus-based immunosuppression regimen among Iranian liver transplant patients while intravenous tacrolimus had not been imported to this country yet, SOT pharmacists resolved the clinical problem for liver transplant patients who could not swallow the drugs for a few days after transplantation surgery by sublingual administration of tacrolimus based on the results of a local study in these patients (7). During daily rounds, the SOT pharmacist realized that the nephrologists of IKHC kidney transplant center act differently on CNI modification of kidney transplant recipients who experienced delayed graft function (DGF). Therefore, a clinical trial was conducted to clarify whether delayed initiation of CNI may decrease the incidence or duration of DGF among these patients. Based on the findings of this trial, the immunosuppressive protocol of the center was regulated to initiate CNI soon after transplantation with no delay to several days post transplantation (8). Considering advantages and disadvantages of glucocorticoids as maintenance immunosuppressive regimen (9), several years of internal experiences with (methyl) prednisolone in maintenance immunosuppressive regimens of the center and external studies, SOT pharmacists fastened the rate of steroid tapering in pharmacotherapy protocols of IKHC for liver, kidney and simultaneous-kidney pancreas transplant patients (10-14). Another dose finding and drug regimen modification that was implemented by SOT pharmacists was rabbit anti-thymocyte globulin (rATG) induction dose for kidney transplant patients. Due to the moderate to high immunologic risk of most kidney transplantation cases in Iran and unavailability of basiliximab, rabbit anti-thymocyte globulin (rATG) induction therapy is applied for almost all kidney transplant recipients from deceased donors in Iran. At the beginning of the participation of SOT pharmacists in transplant wards, they found that cumulative administered doses of rATG as induction immunosuppressive therapy was 6 to 10mg/kg body weight for almost all patients, while the higher part of this range used to be prescribed for patients who experienced DGF. With a systematic review and meta-analysis, SOT pharmacists revealed that lower rATG cumulative doses of 3 to 4.5mg/kg are as effective as higher doses as induction therapy, but exert less ADRs. Thereafter, the immunosuppressive protocol of the IKHC kidney transplant center adjusted accordingly (15). In addition to cost-saving of this immunosuppression modification, the potential dose-related hematologic side effects of rATG would decrease (16, 17). Since hematologic side effects (leukopenia, thrombocytopenia and anemia) are very common among SOT patients and may be the side effects of different immunosuppressive and non-immunosuppressive medications commonly used by transplant recipients, an algorithmic approach for management of cytopenia after SOT and stepwise manipulation of offending drugs were published by SOT pharmacists to optimize ADRs management while reducing the risk of allograft rejection or infections due to rapid withdrawal of some immunosuppressive or antimicrobial drugs respectively that are deemed to be responsible for observed hematologic ADRs (18).

In addition to vigilance for occurrence and management of common ADRs of immunosuppressive and non-immunosuppressive drugs among transplant recipients in everyday rounds, SOT pharmacists also seek late-onset and overlooked ADRs (19) or signals of unpredictable or poor-recognized ADRs. As an example, during several months, three cases of liver transplant recipients with Pneumocystis jirovecii pneumonia (PJP) were admitted at IKHC liver transplant ward. This phenomenon was rare beforehand. The SOT pharmacist suspected the role of inhibitors of mammalian Target of rapamycin (mTOR) that had been recently included in maintenance immunosuppressive protocols of some patients in the ward. This suspicion was strengthened by performing a systematic review and meta-analysis (20). Based on this finding, duration of PJP prophylaxis using cotrimoxazole was expanded from 6 to 12 months for patients whose immunosuppression regimen contained mTOR inhibitor in IKHC transplant center (10, 12).

Transplant pharmacists in this center carefully detect

any drug interactions between immunosuppressive drugs with other drugs, food, supplements, herbal remedies, and laboratory tests and manage them. A few less-recognized drug interactions were detected and published by SOT teams of IKHC. Nephrologists of IKHC kidney transplant center used to administer oral conjugated estrogen with daily doses of 1.875 to 3.75 mg daily from 1-2 days before to 1 day after kidney biopsy of renal transplant patients, a practice that was not common worldwide. Using TDM, SOT pharmacists detected increased tacrolimus blood concentrations among these patients and confirmed this interaction using a case-control study (21) that was cited by popular international drug interaction data bases (22). They also criticized drug interactions between some immunosuppressive medications (i.e., tacrolimus) and direct acting oral anticoagulant drugs that had been reported to be of major importance by American Heart Association and provided evidence that this new class of anticoagulant drugs can be taken safely by tacrolimus users who needs these antithrombotic agents (23).

Clinical transplant pharmacists at IKHC center are also actively involved in designing treatment regimen for less commonly encountered clinical situations. As an example, anti-body mediated rejection is uncommon among liver transplant patients in contrast to kidney recipients; therefore, liver transplant teams have fewer experiences for treatment of these patients. In IKHC center, SOT pharmacists did a systematic literature review on management of cases of liver transplant recipients with AMR. Using this systematic review and internal experiences, they provided an algorithm for treatment of these transplant patients (24, 25).

Drug dose adjustment based on the level of kidney or liver function is another responsibility of SOT pharmacists. Drug dosing after kidney transplantation remains a major problem. During the first few days after transplantation, rapid decrease in serum creatinine concentrations makes using common formulas such as Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) unreliable for evaluation of kidney function. Interaction between demographic data of kidney donor versus those of recipient remains unknown. On the other hand, some patients may experience delayed or slow graft function which makes drug dose adjustment more complicated (26, 27). The rate of acute or acute on chronic kidney injury is very high among liver transplant recipients, therefore, similar problems in drug dosing may happen for liver transplant patients (28). These discrepancies in drug dose modification highlight the importance of consistent presence and research activities of SOT pharmacists.

Finally, the Iranian SOT pharmacists in close collaboration with other members of multidisciplinary transplant team including surgeons, gastroenterologists, infectious disease specialists, nephrologists, and nurses and using internal data and doing systematic-review with or without meta-analysis have developed local and national comprehensive pharmacotherapy protocols for different types of solid organ transplantations for adults and pediatric patients. These protocols, which are published as books in Persian language and some parts of them are published as review articles in peer-reviewed journals, cover almost all aspects of pharmacotherapy requirements pre-, peri-, and post-transplantation for healthcare providers, patients and their caregivers. Some covered aspects include different immunosuppressive protocols (induction and maintenance immunosuppressive therapy, treatment of acute cellular and antibody mediated allograft rejection), prophylaxis and treatment of infections, vaccination, prevention and treatment of thromboembolic events peri-transplantation, detection and management of ADRs, detection and management of drug interactions, safe life style and nutrition, drug considerations and modifications before and during pregnancy and breast-feeding, and extemporaneous drug preparations for children or tube-fed patients (9-15, 18, 20, 24, 29-31). SOT pharmacists are a proactive group of SOT teams. With the start of COVID-19 pandemic, Iranian transplant pharmacists rapidly get transplant recipients under observed (32) and prepared an internal protocol for modification of immunosuppressive therapy of SOT patients with COVID-19 (33).

Post-transplantation phase

A medication therapy management clinic for SOT patients will be launched at IKHC starting October 2023. The duties of SOT pharmacist in this outpatient clinic are periodic visits of SOT recipients to find any drug-related problems, developing action plans accordingly for the health-care team and patients in close collaboration with transplant physicians, preparing and updating patients' medication record, and using different educational and technological methods to improve SOT patient's adherence to their medication therapy.

Development of SOT pharmacotherapy services in Iran

The second SOT pharmacotherapy service was established in Abu-Ali Sina Hospital, Shiraz in 2017. Now, at least

eight transplant centers in different cities of Iran (Tehran, Shiraz, Esfahan, Tabriz, Ahvaz, Urmia) have clinical transplant pharmacists in their multidisciplinary team.

Future perspective

Board Certification in Solid Organ Transplant Pharmacotherapy (BCTXP) was established in 2018 in the US as a mechanism to identify and recognize specialty knowledge and expertise within the field of SOT pharmacotherapy. The aim of this postdoctoral program is providing SOT pharmacotherapy services for all patients from pre-transplantation era to decades after transplantation event in community and hospitals. SOT pharmacists exert varieties of clinical, educational, research, and administrative roles (3). Inspiring that, SOT pharmacotherapy fellowship has been programmed in Tehran University of Medical Sciences and is under consideration by National Board of Clinical Pharmacy and Ministry of Health and Medical Education of Iran. Hopefully, this program will be initiated with the first applicants among board certified clinical pharmacists from Fall 2024.

Conflict of interest:

There is no conflict of interest to declare.

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