Chapter

Role of the Transplant Pharmacist

Megumi Ikura, Kazuki Nakagita, Takaya Uno, Hiromi Takenaka, Sachi Matsuda, Miho Yoshii, Rikako Nagata, Ichiro Nakakura, Naoki Hayakawa, Tsutomu Nakamura, Kyoichi Wada and Osamu Seguchi

Abstract

At the National Cerebral and Cardiovascular Center, Japan, pharmacists have been involved in drug treatment management and patient care as members of multidisciplinary heart transplant teams that include surgeons, physicians, recipient transplant coordinators, and nurses during the waiting period for heart transplantation (HTx), HTx surgery, and post-HTx. During the waiting period, pharmacists play an important role in adjusting the use of antibiotics, anticoagulants, and antiarrhythmics by patients receiving a ventricular assist device (VAD). During HTx surgery and post-HTx, pharmacists advise physicians regarding the individualized medication protocol for immunosuppression and infection prevention to be used for each patient based on the patient's pre-HTx characteristics as well as gene polymorphisms. They thus contribute to reducing the burden on the physician through the sharing of tasks. Throughout all three phases of HTx, pharmacists repeatedly provide medication and adherence education to the patients and caregivers. It is hoped that an academic society-led training protocol as well as transplant pharmacists will be established in Japan and other developed countries, and that these specialized transplant pharmacists would then provide individualized pharmacotherapy for the use of various antibiotics, anticoagulants, and immunosuppressive agents that have a narrow range of treatment in VAD and HTx patients.

Keywords: transplant pharmacist, individualized therapy, patient education, immunosuppressive agents

1. Introduction

In1997, the Act on Organ Transplantation was enacted in Japan, and the first heart transplantation (HTx) under the law was performed in 1999 [1]. However, the number of organ donors has been quite low in Japan, and therefore, many HTx candidates have no choice but to travel overseas to seek the opportunity for HTx [2]. Meanwhile, the Declaration of Istanbul was set out at the Transplantation Society in 2008, in which patients awaiting HTx need to wait for donor opportunities in their own countries, sidestepping efforts by many individuals related to organ transplantation to amend and revise the Act on Organ Transplantation in 2010. Over the last decade,

although the number of brain-dead organ donors has increased gradually, the number of patients awaiting HTx has been increasing year by year [2]. Furthermore, the COVID-19 pandemic reduced the frequency of the organ transplantation procedures, and the number of organ donors has decreased. Consequently, the waiting period for HTx has become longer, at 5 years or more in most cases in Japan [3].

At the National Cerebral and Cardiovascular Center (NCVC), Japan, the multidisciplinary HTx team, including surgeons, physicians, pharmacists, recipient transplant coordinators (RTC), nurses, nutritional support teams (NSTs), physical therapists, and medical engineers, has supported the patients during the waiting period for HTx, HTx surgery, and post-HTx. In this situation, pharmacists play the role of a specialist providing pharmaceutical care to patients awaiting HTx as well as heart transplant recipients (HTRs). The pharmacist stationed in the ward participates in morning and evening conferences as a member of the medical team to monitor the patient's daily condition, provides pharmacological management, and actively provides prescription support and patient education, and it is expected that the transplant pharmacist also actively contributes to individualized pharmacotherapy for various patient groups, from those suffering from severe heart failure to those in the post-transplantation phase.

In this chapter, the role and responsibilities of pharmacists are described from the perspective of drug treatment management and patient education in preoperative and postoperative HTx patients, and individualized pharmacotherapy is also discussed.

2. Waiting for an HTx

Patients awaiting HTx have terminal circulatory failure, and ventricular assist devices (VADs), which can mechanically propel blood from the heart to the central circulation and temporarily augment the cardiac output, have been recognized as essential treatment options as "bridge to transplant" (BTT) [1–3]. VADs include intracorporeal or paracorporeal devices, and the former can not only improve the functional status and quality of life of the patients awaiting HTx, but also enable them to return to almost normal lives [4, 5].

On the other hand, VADs often cause pump thrombosis by forming blood clots in the device, and therefore patients receiving VADs require long-term anticoagulation treatment to prevent thromboembolic complications. In addition, although intracorporeal VADs are fully implantable pumps in the body, a driveline attached to the pump penetrates the skin and connects to an external controller and battery, thereby potentially increasing the risk of infectious diseases that may require hospitalization.

At NCVC, intracorporeal VADs have been used in more than 90% of the patients awaiting HTx. The pharmaceutical management and patient education by pharmacists are described below.

2.1 Pharmaceutical management

2.1.1 Warfarin (WF)

Warfarin (WF) is most frequently used as a prophylactic antithrombotic drug after VAD implantation [6]. In general, the dose of WF is routinely adjusted according to the prothrombin time international normalized ratio (PT-INR). At the start of an urgent anticoagulant therapy for VAD implantation, heparin or dalteparin is used in combination

with WF while paying attention to heparin-induced thrombocytopenia until stable PT-INR can be maintained. Meanwhile, antimicrobial agents such as linezolid (LZD), daptomycin (DAP), and levofloxacin, and antiarrhythmic agents such as amiodarone (AMD), may result in drug–drug interactions with WF, which could lead to unexpected anticoagulation and bleeding risk [7–9]. Pharmacists check classical clinical factors (age, sex, weight, height, and concomitant medication) and request the physicians in charge to take blood samples for additional PT-INR monitoring and provide prescription support, if a potential drug interaction between WF and concomitant medication is a concern.

WF produces an anticoagulant effect by interfering with the interconversion of vitamin K (VK) to its reduced form, which is required for γ-carboxylation of several vitamin-K-dependent proteins that regulate blood coagulation [6]. VK is present in many kinds of foods and beverages, and it has been reported that meals affect PT-INR in patients taking WF [7–9]. Therefore, careful attention should be paid to foods and drinks for the control of PT-INR. On the other hand, VK plays an important role in bone formation through activation of osteocalcin as well as maintenance of normal blood coagulation [10, 11], and excessive restriction of VK intake may lead to decreased quality of life. At NCVC, an interdisciplinary NST, composed of physicians, dieticians, pharmacists, and nurses, participates in the routine assessment of the patient's energy, protein, fluid, mineral, and electrolyte requirements as well as vitamins, and pharmacists explain the importance of dietary management to obtain stable PT-INR to the patients receiving VAD and their families/relatives during hospitalization [12]. A certified dietician also controls every HTR's VK intake through the meals not only during hospitalization but also after release from the hospital.

Recently, genetic polymorphisms of genes encoding cytochrome (CYP) 2C9, a metabolic enzyme of *S*-WF, and those of the VK epoxide reductase complex (VKORC1), a target enzyme of WF in vitamin K recycling, have also been reported as key factors affecting the pharmacokinetics (PK) and pharmacodynamics (PD) of WF, respectively. These factors may be useful for the control of PT-INR through dose adjustments [10, 11]. At NCVC, we often observe that some patients with an implanted VAD have difficulties in controlling the dose of WF. In such a case, pharmacists suggest the physician additional tests to determine the genotypes of CYP2C9 and VKORC with the consent of the patient and carefully adjust the WF dosage [11]. Because dose adjustments based on gene polymorphisms are not covered by the universal health insurance system in Japan so far, further evidence-based data accumulation is needed.

Meanwhile, when the patient with VAD undergoes urgent surgery or experiences severe or life-threatening bleeding, the dose of WF should be reduced immediately, and anticoagulation reversal is required. The International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend that anticoagulation therapy should be held in patients with mechanical circulatory support in the setting of clinically significant bleeding [13]. In such emergency cases, in addition to the cessation of WF treatment, intravenous administration of vitamin K2 as an antagonist of the anticoagulant activity of WF and that of human prothrombin complex supplemented with VK-dependent blood coagulation factors are performed to improve the excessively enhanced anticoagulant state.

2.1.2 Antimicrobial agents

During the waiting period for HTx, VAD-associated infections can often be a problem. Pharmacists help physicians select appropriate antimicrobial agents and maintain their dosing adjustments. In addition, pharmacists routinely monitor side effects and sometimes utilize therapeutic drug monitoring (TDM) [14]. LZD and DAP are effective for

Gram-positive bacteria such as *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and others, which are resistant to other antibiotics [15]. However, LZD may induce pancytopenia, which makes it difficult to continue the administration of the drug. DAP is also used to treat various bacterial infections caused by Gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) [16, 17]. As mentioned above, LZD and DAP are also known to interact with WF, and therefore, pharmacists monitor the fluctuation of PT-INR carefully and provide prescription support [18].

2.1.3 Other agents

The administration of cardioprotective drugs such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and/or beta-blockers is essential for patients awaiting HTx, and that of antiarrhythmic agents is an option to treat ventricular arrhythmias. Among these drugs, certain antiarrhythmic agents have the potential to cause drug–drug interactions, and pharmacists should pay careful attention to those.

Antiarrhythmic agents are categorized depending on their mechanism of cardiac action and certain types of arrhythmias, and the Vaughan Williams classification is the most widely recognized system. Vaugham Williams class Ib (mexiletine) and class III (AMD, sotalol) drugs are often administered to patients awaiting HTx. TDM is necessary for the optimal administration of these antiarrhythmic agents [19, 20]. Because AMD can interact with WF, pharmacists need to check side effects on the thyroid and lungs. Sotalol dosing is based on renal function, and a careful approach is recommended for initial dosing and up-titration.

2.2 Patient education

During hospitalization, patients and their families need to be educated that some foods and drinks in daily life may increase drug effects as mentioned above [7–9]. Especially, VK is a typical factor influencing the control of PT-INR in patients taking WF and is usually obtained from green vegetables and vegetable oils as well as VK supplements. In Japan, people also traditionally eat a large amount of boiled vegetables, and often eat *natto*, a traditional fermented food in Japan that produces VK in the intestinal flora. Japanese people tend to consume more VK-containing foods, and the therapeutic effectiveness of WF may be diminished by high VK intake. Therefore, HTRs are free to eat vegetables, but all HTRs are prohibited from eating *natto*, and *chlorella* and *green juice* are also sometimes prohibited throughout the dosing schedule of WF. Pharmacists explain the importance of dietary management to obtain stable PT-INR to the patients receiving VAD and their families/relatives during hospitalization [12]. Meanwhile, medical staffs cannot frequently check PT-INR and laboratory test values after discharge. To allow the patients to be aware of fluctuations in PT-INR values, pharmacists also need to educate them to monitor PT-INR by themselves using CoaguChek® and determine the WF dosage based on the results of the PT-INR scale.

A certain amount of variability can be seen among individual CoaguChek® devices, and therefore, we monitor PT-INR values calculated by blood sampling during patients' hospitalizations. Considering the difference between the CoaguChek® and PT-INR values, we are trying to obtain an optimal scale for WF adjustment.

HTx surgery is not scheduled, and there are restrictions on visiting rooms after the surgery for clean room management. Therefore, pharmacists must explain about

post-transplant medication from the early stage during the HTx waiting period. In addition, pharmacists aim to remove patients' anxiety about pharmacotherapy associated with the change from anticoagulant therapy under heart failure to immunosuppressive therapy and also need to facilitate the introduction of self-managed immunosuppressive medication after transplantation.

3. Perioperative and postoperative HTx

3.1 Pharmaceutical management

3.1.1 Protocol preparation

The protocol for administration of antimicrobials and immunosuppressants during the perioperative period is prepared from the day before to the day of HTx. To create it, pharmacists check the recipient's conditions such as histories of side effects and allergy, laboratory values, preoperative bacterial infection status, viral antibody titer, and current prescriptions and then discuss the need for new or continuous prescriptions. In addition, pharmacists participate in medical staff meetings to confirm donor information including viral antibody titer and preoperative cardiac function and also confirm the timing when the recipient enters into an operating room and determine whether basiliximab should be administered. Basiliximab is not approved for the treatment of HTx in Japan, but a few reports have described the use of basiliximab as beneficial after HTx [21, 22]. Therefore, we usually prepare protocols in case we might use basiliximab for HTRs [23]. The protocol prepared for antibacterial and immunosuppressive therapies created by pharmacists based on this information is shared with cardiac surgeons, cardiologists, and RTCs after approval by the physician in charge.

3.1.2 Immunosuppressive agents

Perioperative immunosuppressive therapy basically consists of a combination of three drugs: calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), and steroids. Alternative immunosuppression strategies are needed for patients with renal impairment, fatal acute cellular rejection (AMR), antibody-mediated rejection (AMR), and infections. Herein, the immunosuppressive strategies are described by dividing it into three therapies: induction, maintenance, and response to rejection.

3.1.2.1 Induction therapy

Basiliximab is a chimeric mouse-human monoclonal antibody that binds to the receptor of interleukin 2 (IL-2), inhibiting the proliferation of T cells, and is approved for the suppression of acute rejection response after renal transplantation in Japan, but not for heart transplantation. Basiliximab has been widely used as an induction therapy in renal transplantation, although the incidence of adverse events, such as cytomegalovirus (CMV) infection, malignancies, or post-transplant lymphoproliferative disorders, is of concern [24].

At NCVC, the standard immunosuppression protocol for HTRs is the regular release tacrolimus (TAC)-based triple immunosuppression therapy. Usually, TAC and MMF are introduced for HTRs immediately after postoperative decannulation and passing the swallowing test. However, TAC has side effects such as nephrotoxicity

and can exacerbate pre-HTx renal dysfunction of the HTR by increasing renal vasoconstriction caused by TAC. In such a patient, the introduction of induction therapy using basiliximab as well as two-week delayed start of administration of TAC is to be considered. To date, in our institute, the effect of induction therapy using basiliximab with delayed TAC administration on the clinical prognosis of HTRs has been verified as compared with that of a standard TAC-based triple immunosuppression therapy [23]. The former therapy might be feasible and safe for HTRs fulfilling certain inclusion criteria including renal function, sensitization for anti-human leukocyte antigen (HLA) antibody, and HTR- and donor-related risk factors, although a comprehensive evaluation of the clinical necessity of basiliximab-based induction therapy is necessary (see [23] for more detailed inclusion criteria). Basiliximab-based induction therapy is also applied to pediatric HTRs and the patients experiencing long-time aortic blockage.

3.1.2.2 Maintenance therapy

3.1.2.2.1 Calcineurin inhibitors (CNIs)

CNIs such as TAC and cyclosporine (CYA) exert their immunosuppressive effects by reducing interleukin-2 (IL-2) production and IL-2 receptor expression, leading to a reduction in T-cell activation. Briefly, TAC and CYA inhibit T-lymphocyte activation by binding to a member of the immunophilin family, FKBP12 and cyclosphilin, respectively. The complex formed by the drug-binding protein, calcium, calmodulin, and calcineurin inhibits calcineurin-mediated dephosphorylation and subsequent translocation of the nuclear factor (NF) of an activated T cell (NFAT) to the nucleus. NFAT initiates transcription of pro-inflammatory cytokines, including IL-2 and of its receptor. These CNIs also inhibit the activation of other transcription factors involved in IL-2 gene expression in T cells such as NF-kB. Thus, CNIs inhibit a variety of immune functions and have a narrow therapeutic index, meaning that lower exposure to a CNI induces organ rejection, whereas higher exposure induces serious infections and malignancies caused by overimmunosuppression. Therefore, pharmacists need to conduct TDM to adequately design dosage regimens of CNIs.

TAC and CYA are metabolized by the CYP3A subfamily, and many drug interactions with these CNIs reported in the solid organ transplant population are associated with intestinal and hepatic CYP3A. CYP3A is a most important drug metabolizing enzyme that has a wide substrate specificity, and a very large number of drugs are the substrates for this enzyme. Pharmacists routinely check newly prescribed medications in combination with CNIs, especially those on the list (**Table 1**), which are often used in HTRs at NCVC.

AMD is metabolized through the CYP3A metabolic pathway, and it has been reported that patients receiving AMD prior to transplant require a reduction of the TAC dose [25]. It is therefore necessary to check blood levels of both AMD and TAC carefully. Amlodipine, a substrate of CYP3A, is often used to control blood pressure during the perioperative period, and a careful control of the blood concentrations of TAC after the initiation of TAC is needed [26, 27]. Clotrimazole inhibits CYP3A function [28]. To date, oral clotrimazole lozenges have been used for prevention of opportunistic infections at NCVC, but we have experienced a need for dose adjustment of TAC by hospitalization when this drug is discontinued 6 months after HTx [29–31]. Herein, we have switched to oral amphotericin B for treatment, and since then, it has succeeded in maintaining stable pharmacokinetics of TAC [32]. HTRs with nontuberculous mycobacterial (NTM) disease take rifampicin (REP) and macrolides. REP induces the expression of various CYP subfamilies, whereas erythromycin and

Azole	Antimicrobial agents	Calcium channel blocker	Antiepileptic agent
Voriconazole	aminoglycosides	diltiazem	carbamazepine
ketoconazole	rifampicin	nifedipine	phenytoin
fluconazole	rifabutin	nicardipine	
itraconazole		verapamil	
clotrimazole		amlodipine	

Table 1.
A list of medications that pay particular attention to their interaction with TAC during waiting period for HTx, at HTx surgery and post-HTx at NCVC. TAC, tacrolimus; HTx, heart transplantation; NCVC, National Cerebral and Cardiovascular Center, Japan.

clarithromycin (CAM) among macrolides have a potential to inhibit CYP3A4 function and are metabolized by CYP3A4. The concomitant administration of these drugs can have a significant effect on the pharmacokinetics of TAC. For HTRs taking REP or CAM prior to HTx, pharmacists ask the specialists in advance to change from REP to rifabutin and from CAM to azithromycin to prevent worsening of NTM owing to immunosuppressive therapy and also consider the effect of concomitant drugs on the blood concentrations of TAC [33]. Even if the drugs are not used in combination with TAC, it should be noted that in patients taking drugs with a long half-life, such as AMD, before HTx, the drug may remain in the body for a long time post-HTx, thereby possibly affecting the pharmacokinetics of TAC.

Meanwhile, CYP3A5, as well as CYP3A4, is involved in TAC metabolism [34], and single nucleotide polymorphism in the *CYP3A5* gene, *CYP3A5*3* (6986A>G), is associated with alteration in its metabolic activity, thereby affecting the blood concentration of TAC [35]. The *CYP3A5* genotype is a factor to be considered for TAC dose adjustment. At NCVC, pharmacists determine the *CYP3A5* genotype with the consent of the recipient [35, 36]. As shown in the **Figure 1**, compared with the frequencies found by previous studies in the Japanese population, we have not found any significant difference in the frequencies of the genotypes between *CYP3A5*1/*1* or **1/*3* (CYP3A5 expresser) and *CYP3A5*3/*3* (CYP3A5 non-expresser) [37–39].

At NCVC, in the standard triple immunosuppressive therapy, TAC is generally initiated at a dose of 1 mg/day on the first or second postoperative day.

Thereafter, its dosage is adjusted to achieve an initial blood concentration range of 9–12 ng/mL within a week. Standard target trough levels of TAC to be maintained during the first year post-HTx are 9–12 ng/mL. Depending on the type of concomitant drug, the HTR's renal function, and the status of side effects, the dose of TAC is basically increased or decreased in one step with 0.2 or 0.5 mg as single dose, and in some case in two steps.

Meanwhile, as mentioned above, the total clearance of TAC in HTRs with *CYP3A*1/*1* or *CYP3A*1/*3* is considered to be higher than in those with *CYP3A*3/*3*. Therefore, in the former HTRs, it may be better to standardize two-step dose adjustment and also to set the starting dose to twice the standard levels, although this treatment strategy should be verified [26, 35].

3.1.2.2.2 MMF

MMF is an orally administered prodrug of mycophenolic acid (MPA), which blocks *de novo* biosynthesis of purine nucleotides and lymphocyte proliferation by

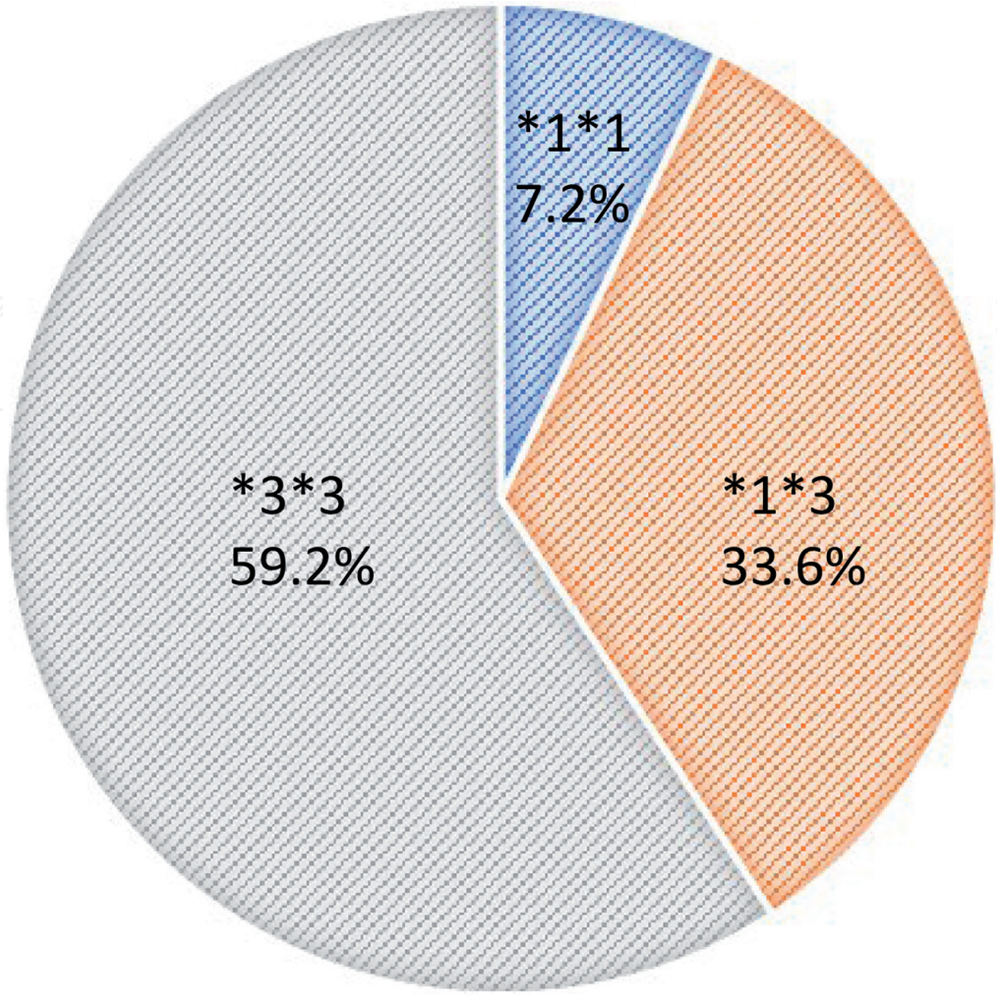

Figure 1.
Distribution of genetic polymorphisms of CYP3A5 in HTRs at NCVC.HTRs, heart transplant recipients; NCVC, National Cerebral and Cardiovascular Center, Japan.

suppressing the enzyme inosine monophosphate dehydrogenase [40]. Concerning MMF, the package insert clearly states that the dosage of MMF varies widely from 500 to 1500 mg per dose. Because the tolerated and effective doses vary from patient to patient, careful adjustment is necessary to achieve optimal therapeutic effects of MPA. In addition, patients with severe renal dysfunction need to be carefully taken care of because the blood levels of MPA can be high [41]. Immediately after HTx, the effects of heart failure are still present, and circulatory conditions are unstable. During this period, the appearance of side effects such as leukopenia should be noted. When the circulatory state has stabilized, pharmacists confirm pharmacokinetics and pharmacodynamics of MPA by area under the blood concentration-time curve (AUC) and make sure there is no rejection based on the myocardial biopsy results.

Diarrhea is one of the adverse effects observed during treatment with MMF [42, 43]. To alleviate it, Chinese herbal medicine *Hangeshashinto* is often used during cancer chemotherapy [44, 45], and it is also expected to be effective against diarrhea caused by treatment with MMF [46]. At NCVC, we additionally administer *Hangeshashinto* to patients treated with MMF, who are free from any suspected infection in the perioperative period or to post-HTx outpatients.

3.1.2.2.3 Steroids

Steroids have anti-inflammatory, immunosuppressive, and lympholytic effects by preventing the production of cytokines and vasoactive substances, including IL-1, IL-2, IL-6, tumor necrosis factor-α, chemokines, prostaglandins, major histocompatibility class II, and proteases. In HTx, methylprednisolone and prednisone are used frequently as part of the immunosuppressive regimen to prevent rejection. Intravenous methylprednisolone is administered at the initiation of the transplant procedure, and the dose is repeated until 3 weeks after the HTx. Thereafter, the steroid dose is gradually reduced until completion of 5 weeks post-HT, although methylprednisolone is switched to oral prednisolone if cardiac allograft rejection is not found at the myocardial biopsy after 3 weeks post-HTx.

Meanwhile, side effects are often a problem when using steroids, and pharmacists need to be aware of patient complaints and clinical findings. Delayed wound healing, diabetes, and gastric ulcer are often found in the postoperative acute phase, and osteoporosis, cataracts, hypertension, depression, and growth retardation are long-term problems.

At NCVC, HTRs are hospitalized for routine endomyocardial biopsies to assess graft rejection, coronary angiography, and coronary intravascular ultrasound with the development of cardiac allograft vasculopathy. If cardiac allograft rejection is not observed in the myocardial biopsy, the dose of steroid is tapered over 6–12 months before its discontinuation, except for HTRs with cardiac sarcoidosis who are treated with low-dose prednisolone. Meanwhile, if cardiac allograft rejection was detected in a regular myocardial biopsy after HTx, the patients are treated with augmented immunosuppression and intravenous steroids, and we consider the oral dose of steroid after the steroid pulse therapy.

We manage pediatric patients to decrease the dose of steroid or terminate steroid use as early as possible considering their healthy growth.

3.1.2.2.4 Everolimus (EVL)

Everolimus (EVL) is an inhibitor of the mammalian target of rapamycin (mTOR), a phosphatidylinositol 3-kinase-related kinase, and plays a central role in the regulation of many cellular functions including growth, proliferation, and survival [47]. EVL are usually introduced in HTRs during the maintenance phase after HTx and are often used by switching from or adding to MMF. Meanwhile, EVL can cause poor wound healing, and its initiation should be delayed up to about 2 months after surgery. The major reasons for the switching or adding are as follows: (1) post-transplant cardiac allograft vasculopathy (CAV) progression; (2) reduced renal function; and (3) malignant tumor complications, especially post-transplant lymphoma (PTLD). In an international consensus report, a target trough EVL concentration of 3–8 ng/mL was proposed [48], while paying attention to adverse events including hyperlipidemia, wound infection, acne-like skin lesions, and leukopenia. Meanwhile, EVL is a substrate of the CYP3A metabolic enzyme, and when used in combination with a CNI, the blood concentrations of the CNI need to be adjusted to 2/3 to 3/4 and sometimes 1/2, before concomitant use. Pharmacists herein prepare to renew the dosing regimens of EVL as well as CNI, which can contribute to reduce the burden on the physician. In the event of EVL introduction, the EVL protocol is prepared upon physician's request, and EVL blood concentration is monitored once or twice a week after EVL initiation, followed by myocardial biopsy approximately one month after EVL introduction. When preparing the EVL protocol, information on the rationale for the change of regimen

and optimal blood concentration of EVL is collected from the physician, and then the change of regimen and the schedule of visiting the hospital for the collection of blood are explained to the patient. After the start of EVL administration, there are concerns about the occurrence of stomatitis. The pharmacists instruct the HTRs to maintain the mouth clean and to use dexamethasone ointment and azulene sulfonic acid as a treatment when stomatitis occurs. The blood concentration level of TAC and EVL is carefully monitored considering the competitive interaction with FK-binding protein.

3.1.2.3 Response to rejection

Rejection after HTx includes acute rejection immediately after surgery, acute cellular rejection (ACR) that may occur within a few weeks to 2 years post-HTx, and CAV after those. It is also classified into cellular rejection, antibody-related rejection (AMR), and mixed type according to the mechanism of onset. Among them, AMR has been paid attention to during maintenance immunosuppressive therapy after HTx.

For AMR, the following treatments can be considered: (1) plasmapheresis to remove antibodies from the circulation; (2) intravenous immunoglobulin therapy and anti-CD20 monoclonal antibody (rituximab) to suppress antibody production; (3) use of corticosteroids to suppress the inflammatory response; (4) change of immunosuppressive therapy (use of cyclophosphamide and change from CYA to TAC) and/or dose adjustment of immunosuppressive agents; and (5) use of antithymoglobulin to suppress helper T cells.

3.1.3 Prevention of infectious diseases

Because HTRs receive immunosuppressive therapy, sufficient prophylactic treatment against infections is necessary soon after HTx. Perioperative antibiotic therapy is selected based on microbiologic sensitivities. Prophylactic treatment for bacterial infections includes broad-spectrum drugs against Gram-positive and Gram-negative bacterium, such as LZD and doripenem. MRSA and fungal infections may also be problematic in patients bridged from VAD to HTx. Intravenous antifungals such as micafungin (MCFG) are administered for fungal infections. MCFG intravenous infusion is changed to AMPH B gargle after passing the drinking water test and continued for 6 months after HTx. To prevent opportunistic infection, HTRs receive anti-*Pneumocystis* prophylaxis with sulfamethoxazole/trimethoprim for life, and the dose is adjusted depending on the HTR's renal function. Cytomegalovirus (CMV)-seropositive HTRs are routinely administered CMV immunoglobulin immediately after the HTx, which is continued until 5 days post-HTx. In CMV-seronegative HTRs transplanted with organs from CMV-seropositive donors (CMV mismatch), anti-CMV drugs such as ganciclovir or its prodrug valganciclovir are administered prophylactically at half the therapeutic dosage within 10 days of HTx and are continued until 1 year after the HTx at NCVC. If the results of CMV antigenemia and real-time polymerase chain reaction tests are positive, an anti-CMV drug is initiated at a therapeutic dose (900 mg/day) in cases with clinical symptoms or as preemptive therapy in asymptomatic cases when CMV DNA exceeded the threshold set for active CMV infection. The dose of the anti-CMV drug is adjusted according to the patients' conditions such as renal function.

3.2 Patient education

After HTx, immunosuppressive therapy and prevention of opportunistic infections are in essence supported by the recipient's adherence to medication, and patient

education is essential to ensure adherence and understanding of the need for lifelong pharmacotherapy. Patient education should start during the transplant waiting period and continue after HTx until the patient can self-manage by the time of discharge.

MMF is teratogenic and requires a contraceptive period of 6 weeks after discontinuation as well as during administration. Therefore, pharmacists need to educate potentially pregnant recipients on contraception.

If HTRs wish to give birth, the use of MMF and mizoribine is avoided, and it is switched to immunosuppressive therapy based on CNI and azathioprine use because MMF and mizoribine are known to be teratogenic. In addition, ACEIs and ARBs, which are administered as antihypertensive agents and cardiac protective agents, have also been reported to cause oligoamnios or increase the risk of teratogenicity. In such a case, we consider administering methyl-dopa as an antihypertensive agent as needed and changing to nifedipine after 20 weeks of gestation [49].

4. After discharge from HTx

4.1 Pharmaceutical management

HTRs who have passed the acute postoperative stage are treated in cooperation with hospitals near their homes, taking into consideration their return to society. In our institute, pharmacists provide continuous support for the dose adjustment of immunosuppressive drugs from our hospital to the collaborating hospital after discharge through fax and e-mail communication. However, there are sometimes inter-institutional differences in the results of immunosuppressant blood concentration owing to different measurement methods. Therefore, pharmacists need to confirm the measurement method with each collaborating hospital in advance to adjust the dose of immunosuppressant accordingly.

When patients are prescribed a new drug at a hospital or clinic, they are instructed to contact the RTC and ask for instructions on whether or not they can take the prescription medications. The RTC informs the physician and pharmacist about the new prescription drugs and the patient's condition, and then the pharmacist evaluates possible interactions between the new prescription drugs with the drug the patient is taking, especially immunosuppressive drugs. If interactions that affect the efficacy of the immunosuppressive drugs are expected, the pharmacist provides and shares the information with the physician. If the physician decides that the patient needs to continue taking the immunosuppressive drugs despite the interaction, the pharmacist recommends when to check their blood concentrations as needed.

4.2 Patient education

4.2.1 Patient education for therapy adherence

The main role of transplant pharmacists after discharge of the patient from the hospital is as follows: management of immunosuppressive therapy and infections during outpatient visits; guidance to improve medication adherence; and the development of protocols for dose adjustment and change of immunosuppressive agents as renal function deteriorates and CAV occurs. In particular, when changing the immunosuppressive agents, pharmacists have to explain the need to change the drug and the accompanying need for blood sampling to the patients and also instruct the patients to contact their local pharmacies to share the new protocols.

When patients return to society, they often have difficulties in taking their immunosuppressant medications on time owing the time and means of commuting to school or work. In such a case, pharmacists support the patients by shifting the time of taking the medication and also instruct them to pay attention to the time of blood collection before taking the medicine during outpatient visits.

CYA-associated side effects include hirsutism and gingival thickening. Hirsutism has cosmetic problems, especially for women and adolescents, and may reduce adherence to medication. In addition, gingival thickening, especially in infants, interferes with the subsequent development of teeth, and in some cases, repeated gingivectomy may be required. In this case, switching from CYA to TAC is a treatment option.

4.2.2 Diet and lifestyle

Diet and lifestyle are important from the perspective of CAV prevention, and nutritionists provide the patients with guidance about these points during hospitalization. In addition, hyperglycemia and hyperlipidemia have been reported as side effects of immunosuppressive drugs, and pharmacists provide guidance on diet and lifestyle precautions from the perspective of these side effects. To avoid and reduce interaction with immunosuppressive agents, pharmacists should explain what foods HTRs need to be aware of and why and instruct them to avoid their intake. Such foods and diet are dietary supplements, herbal medicines, herbal teas, and grapefruit juice [50]. Meanwhile, immunosuppressive agents are taken as time-release drugs and should be taken continuously at a set time. For this reason, pharmacists also make HTRs understand the importance to maintain a regular life rhythm.

5. Other relevant aspects

5.1 Individualized therapy

Although various factors such as concomitant medications, diet, and lifestyle can influence the pharmacokinetics of immunosuppressive agents and WF, genetic polymorphisms also need to be taken into consideration as variable factors affecting the pharmacokinetics of immunosuppressive drugs and WF during HTx waiting time and after HTx. Pharmacists need to collect and organize information about such variable factors that cause inter-individual or intra-individual fluctuations of these drugs in HTx patients and provide them to physicians. This contributes to not only individualized therapy, but also to reduce the burden on physicians and enable task sharing.

5.2 Certification of transplant pharmacists

In the United States, the Doctor of Pharmacy (Pharm.D.) degree was established in the 1950s, and the American Society of Hospital Pharmacists introduced a residency program in the 1960s that transformed the role of pharmacists in team medicine [51]. In organ transplantation, the specialty pharmacist system was accredited in 2018, and guidelines for pharmacist services and education have been developed [52].

The Canadian Hospital Pharmacists Association reported on the expertise of transplant pharmacists in 2018 [53].

6. Conclusions

Transplant pharmacists at each hospital have built up their own expertise and are participating in medical teams at each facility, playing a role in organ transplantation. Because transplantation medicine requires individualized medical care, there are many situations in which pharmacists can contribute. As a member of the medical team, transplant pharmacists are involved in anticoagulation and immunosuppressive therapy and provide prescription support, which not only reduces the burden on physicians, but also contributes to the promotion of effective and safe use of drugs. Transplant pharmacists as well as members of NST, infection control teams, or palliative care teams can contribute to healthcare economy and healthcare safety by taking the initiative of appropriate use of agents.

Meanwhile, it is hoped that an academic society-led transplant pharmacist will be established, and that specialized transplant pharmacists can provide individualized pharmacotherapy for antibiotics, anticoagulants, and immunosuppressive agents, which have a narrow range of treatment in the field of VAD and HTx treatment in Japan as well as other developed countries.

Conflict of interest

The authors declare no conflict of interest.

Author details

Megumi Ikura[1*], Kazuki Nakagita[1], Takaya Uno[1], Hiromi Takenaka[1], Sachi Matsuda[1], Miho Yoshii[1], Rikako Nagata[1], Ichiro Nakakura[1], Naoki Hayakawa[1], Tsutomu Nakamura[2], Kyoichi Wada[2] and Osamu Seguchi[3]

1 Department of Pharmacy, National Cerebral and Cardiovascular Center, Suita, Japan

2 Education and Research Center for Clinical Pharmacy, Faculty of Pharmacy, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

3 Department of Transplant Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

*Address all correspondence to: ikura.megumi48@ncvc.go.jp

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