Biomedicine & Pharmacotherapy 102 (2018) 107–114

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Current progress of tacrolimus dosing in solid organ transplant recipients: Pharmacogenetic considerations

Xiao Zhang[a,1], Guigao Lin[b,c,1], Liming Tan[a,*], Jinming Li[b,c,**]

[a] Department of Laboratory, First Affiliated Hospital of Hunan Normal University, The People's Hospital of Hunan Province, Changsha, Hunan, China
[b] National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology, Beijing, China
[c] Beijing Engineering Research Center of Laboratory Medicine, Beijing, China

ARTICLE INFO

Keywords:
Cytochrome P450
Tacrolimus
Pharmacogenetics
Therapeutic drug monitoring
Algorithm
Clinical decision support

ABSTRACT

Tacrolimus is effective for the prevention of acute rejection, but is also highly toxic and has great intra- and inter-individual variability in transplant patients. Genetic variation and other factors influence the response of an individual to tacrolimus treatment. Therefore, even if therapeutic drug monitoring is universally applied, rejection and toxicity still occur. Although the appropriate action on pharmacogenomic variability provides a cornerstone for the precise tacrolimus prescription, at present there are many obstacles to translating it into clinical practice. Pre-emptive genotyping is rarely performed because of practical and financial reasons. However, as the cost of sequencing continues to fall, it is feasible to span all clinically actionable genotypes and provide patients with relevant information throughout their lifetime, which would, therefore, optimize tacrolimus dosing by facilitating the structured dosing algorithms (for example, population pharmacokinetic models) and clinical decision support. In this review, we discuss the current challenges and opportunities for the translation of pharmacogenetic information of tacrolimus into clinical settings.

1. Introduction

Tacrolimus is the most widely used calcineurin inhibitor in solid organ transplantation (SOT), but its application is limited by the wide range of intra- and inter-individual pharmacokinetic variability observed [1]. Thus, therapeutic drug monitoring (TDM) is routinely conducted to maintain the target range and to avoid overexposure or underexposure, with a trial and error approach still a common practice [2,3]. Genetic variations, which significantly affect tacrolimus dose requirements and systemic exposure in SOT patients, are thought to be an important factor in the prediction of tacrolimus dosage [4]. The pre-emptive genotyping and selection of the optimal starting dose based on the genetic background of the patient is rarely performed in clinical practice because of the lack of formal proof of improved clinical outcome [2,5]. However, as inexpensive multigene tests arise, there will no longer be a question over the routine genotyping of SOT patients, but new concerns about how to use and maximize the benefit from the available pharmacogenetic information will prevail.

2. Drug: tacrolimus

Tacrolimus gained FDA approval as an antirejection medication for liver transplantation in 1994. It exerts immunosuppressive effects by binding to its cytoplasmic protein receptor, FK binding protein 12, in T lymphocytes, to form a complex that binds calcineurin, thus preventing nuclear factors from dephosphorylation and nuclear translocation, ultimately inhibiting IL-2 production and T lymphocyte activation [1] (Fig. 1). Cytochrome P450 3A (CYP3A) subfamilies CYP3A4 and CYP3A5 mediate the bio-transformation of tacrolimus through the demethylation and hydroxylation of hepatic and intestinal CYP3A isoforms, and then tacrolimus is cleared through hepatic metabolism [6]. Tacrolimus is also a substrate for the multidrug efflux transporter P-glycoprotein (Pgp, a product of the multidrug resistance 1 gene [*MDR1*] or the ATP-binding cassette transporter [ABCB1]), which interfere with

Abbreviations: ABCB1, ATP-binding cassette subfamily B member 1; ABCC2, ATP-binding cassette subfamily C member 2; CDS, clinical decision support; CPIC, clinical pharmacogenetics implementation consortium; CYP, cytochrome P450; MDR 1, multidrug resistance 1 gene; EHR, electronic health records; eMERGE, electronic medical records and genomics; MLR, multivariate linear regression; IL, interleukin; NGS, next generation sequencing; PGRN, pharmacogenomics research network; POR, cytochrome P450 oxidoreductase; popPK, population pharmacokinetic; SNP, single-nucleotide polymorphism; SOT, solid organ transplantation; TDD, total daily dose; TDM, therapeutic drug monitoring

* Corresponding author at: National Center for Clinical Laboratories, Beijing Hospital, 100730, No.1 Dahua Road, Dongdan, Beijing, China.
** Corresponding author at: First Affiliated Hospital of Hunan Normal University, The People's Hospital of Hunan Province, 410005, No.61 Jiefang West Road, Changsha, China.
E-mail addresses: tanliming838@163.com (L. Tan), jmli@nccl.org.cn (J. Li).
[1] Both authors contributed equally to this manuscript.

https://doi.org/10.1016/j.biopha.2018.03.054
Received 11 December 2017; Received in revised form 27 February 2018; Accepted 9 March 2018

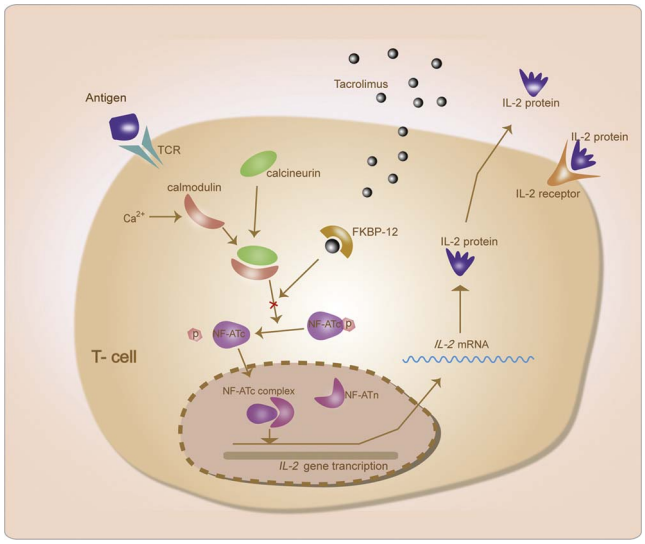

Fig. 1. Mechanism of action of tacrolimus.
Abbreviations: FKBP-12, immunophilin FK- binding protein 12; mRNA, messager ribonucleic acid; NF-Atc, nuclear factor of activated T-cells; p, phosphate; TCR, T-cell receptor. Tacrolimus binds to its cytoplasmic protein receptor, FK binding protein 12, in T lymphocytes to form a complex that binds calcineurin, thus preventing nuclear factors from dephosphorylation and nuclear translocation, ultimately inhibiting IL-2 production and T lymphocyte activation.

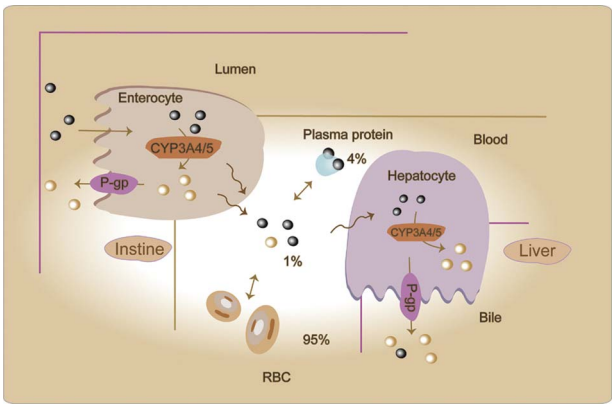

Fig. 2. Absorption, blood distribution and hepatic metabolism and excretion of tacrolimus.
Black circles represent parent tacrolimus; orange circles represent metabolites. RBC: red blood cells. Percentages correspond with the approximate distribution of tacrolimus in blood.

the distribution of tacrolimus throughout the body and its excretion into bile and urine [7]. Tacrolimus distributes from plasma to red blood cells rapidly with a blood: plasma ratio of 13–114:1. The remaining fraction is highly bound to the plasma protein with an unbound fraction of 1% that determines the biological effects and extent of hepatic extraction. Target blood cells like lymphocytes contain a fraction of 0.5–5%(Fig. 2) [8]. A complex interplay among genetic polymorphisms, ethnicity, drugs, herbs, food constituents, endogenous substances, such as uremic toxins, intestinal pathology, liver and kidney disease, hypoalbuminemia, anemia, aging, and formulation determine tacrolimus exposure [9].

Tacrolimus was reported to be more effective than cyclosporine for renal and liver transplantations in several multicenter studies [10,11]. Its use has expanded to other organ types of transplant, such as heart, lung, and hematopoietic stem cell transplant [12–14], and other types of immune-mediated diseases, including psoriasis, steroid-resistant nephrotic syndrome, ulcerative colitis, lupus nephritis, and myasthenia gravis. It has become the first-line treatment for steroid-resistant nephrotic syndrome(SRNS) because of higher effectiveness and less side-effects compared to cyclosporine [15,16]. It was approved for steroid-resistant ulcerative colitis treatment under the national health insurance in July 2009 [17], and are considered to be the second line treatment in patients who have no response to 5-aminosalicylic acid (5-ASA) or corticosteroids [18]. Tacrolimus remains to be a treatment alternative in lupus nephritis(LN), although uncertainties still exist and well-designed trials are required to define the role of tacrolimus in this disease [19]. Despite that available randomized controlled trial evidence does not support the use in myasthenia gravis(MG), tacrolimus was recommended in several national MG treatment guidelines [20–24]. Topical tacrolimus is also considered a first line of therapy for intertriginous psoriasis [25].

3. TDM of tacrolimus and its limitations

Routine TDM in clinical practice is required to maintain tacrolimus blood concentrations within the therapeutic range [6]. Renal transplant recipients usually receive a standard, bodyweight-based tacrolimus starting dose of 0.1 mg/kg twice per day. The drug concentrations are measured multiple times in the first few weeks after the initiation of treatment [3]. The target whole-blood trough concentration (C_0) is between 10 and 15 ng/mL in the early period after transplantation, 5–15 ng/mL after 3 months, and 5–10 ng/mL after 12 months, although there are significant variations around these ranges [26].

Although TDM may help in the adjustment of subsequent doses based on blood concentration, concentration monitoring is not completely suitable. Many factors may interfere with the efficacy of TDM. The age of the patient, transplanted organ type, biomarkers of tacrolimus exposure, time after transplantation, use of concomitant drugs, and the compliance of the patient influence the efficiency of TDM. Most transplantation centers use C_0 to adjust the tacrolimus dosage regimen, although the best marker of drug exposure is the area under the concentration–time curve (AUC) [27]. AUC is used less frequently because of the financial and practical reasons (the requirement of between 8 and 12 blood specimens) [27]. The relationship between C_0 and AUC is still controversial. It was reported that tacrolimus concentrations 5 h post-dose (C_5) whole-blood concentration has a better relationship with $AUC_{0\text{-}6h}$ [28], whereas other studies suggested a stronger correlation between tacrolimus C_3 or C_4 whole-blood concentrations and $AUC_{0\text{-}12h}$. Furthermore, C_0 is characterized by a significant between-patient (20–60%) and within-patient (10–40%) variability [27], therefore, the achievement of target blood concentration does not mean efficacy or the removal of adverse events owing to the individual variability and target concentration variability among different organ types [29]. Moreover, many of the changes in whole blood concentration result from alterations in the blood distribution of tacrolimus that are related to hematocrit and plasma protein, which have no effect on unbound levels [9]. In addition, TDM provides no information on the optimal starting dose of tacrolimus.

4. Pharmacogenetics

Genetic variants play an important role in the large variation in response to tacrolimus therapy. The SNPs in genes encoding metabolizing enzymes CYP3A4/5, contributes to most of the variability in CYP3A expression and tacrolimus dosing requirement [30]. *CYP3A5* is the rather dominant form that explains 40–50% tacrolimus dose response variability [31]. Additional genetic variants, including SNPs in genes encoding membrane transporters such as *ABCB1* and *ABCC2*, and other enzymes/receptors *POR*28* and *PPARA* have been described in the literature with potential effects on tacrolimus metabolism [6].

4.1. CYP3A5

CYP3A5 expression is highly polymorphic, with 25 allelic variants