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Invited critical review

Therapeutic drug monitoring of immunosuppressants by liquid chromatography–mass spectrometry

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ABSTRACT

Immunosuppressant medications allow the transplantation of tens of thousands of allografts per year and consequently have great potential to decrease patient morbidity and mortality. However, some medications have great risk associated with over- and under-dosing leading to adverse effects or allograft rejection, respectively. This necessitates immunosuppressant therapeutic drug monitoring accomplished by immunoassay or liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS). The former's accuracy can be hindered by metabolites of immunosuppressant medications, antibodies against these medications and heterophilic antibodies. Although LC–MS/MS has superior specificity which allows it to be less susceptible to interference, this methodology lacks standardization and the necessary throughput. Recent developments in LC–MS/MS quantitation, however, include patient-friendly sample submission as dried blood spots, higher sample throughput and commercialization. Here we critically review recent LC–MS/MS publications (January 2010 to July 2015) on the quantitation of cyclosporine A, tacrolimus, sirolimus and everolimus.

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1. Introduction

Immunosuppression is crucial to successful transplantation via preventing acute and chronic rejection. However, selection of immunosuppressant regimens is challenging due to complications including drug-specific toxicities, opportunistic infections, and malignancy [1].This critical review focuses on literature since 2010 in the vital field of therapeutic drug monitoring (TDM) of immunosuppressants, and is limited in scope to only 4 commonly prescribed immunosuppressant medications: cyclosporine A, tacrolimus, sirolimus (rapamycin), and everolimus (Fig. 1). A brief background of these medications and the need for TDM are provided. TDM for immunosuppressants is achieved by either immunoassay or liquid chromatography–tandem mass spectrometry (LC–MS/MS). The

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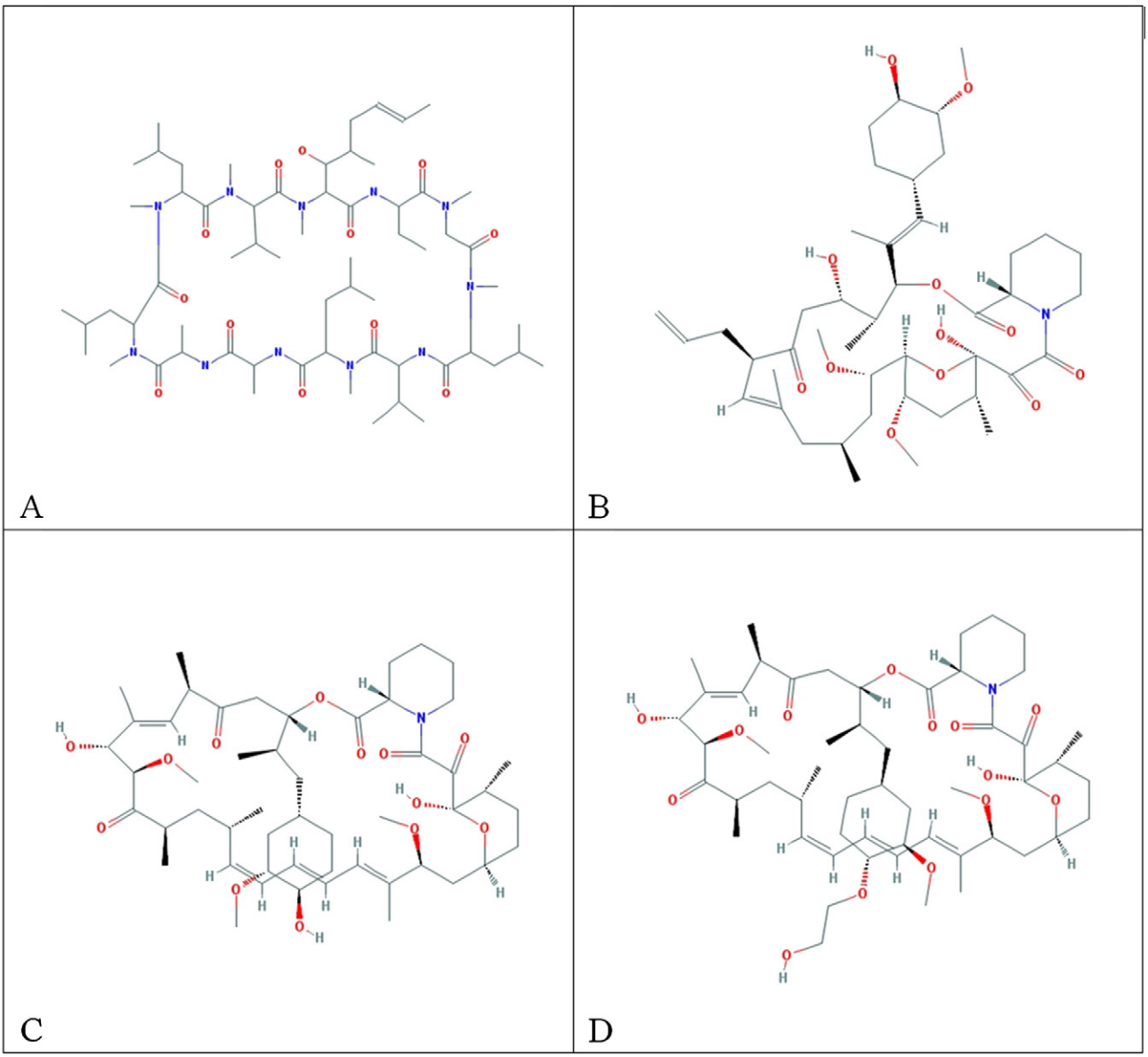

Fig. 1. Structures of (A) cyclosporine A, (B) tacrolimus, (C) sirolimus, and (D) everolimus [57].

analytical aspects of the 2 platforms are considered in detail. Topics covered include deficits of both platforms, recent developments of both methods, and a brief perspective.

1.1. Immunosuppressants in organ transplantation

Immunosuppressant medications are used, amongst other things, to prevent allograft rejection in organ transplant patients. These medications exhibit a suppressive action on the immune system in the hope of preventing organ rejection. Four common, immunosuppressant medications are detailed herein. Cyclosporine A, an 11 amino acid metabolite of *Tolypocladium inflatum*, is a calcineurin inhibitor [2,3]. Tacrolimus, another calcineurin inhibitor, is a macrolide antibiotic from *Streptomyces tsukubaensis* [4]. Sirolimus is a macrocyclic fermentation product of *Streptomyces hygroscopicus* and a mammalian target of rapamycin (mTOR) inhibitor. Lastly, everolimus is a derivative of sirolimus with the same inhibitory target [5].

1.2. Therapeutic drug monitoring (TDM)

For immunosuppressants, a balance needs to be struck between the medication's therapeutic and adverse effects. Unfortunately, the therapeutic ranges for these 4 medications are generally narrow, which is further complicated by unpredictable drug concentrations in the patient's blood. A multitude of variables can contribute to any medication's unpredictable pharmacokinetics [6–8], but variations specific to immunosuppressants include age [9–11], drug–drug interactions [12], race [13], and sex [14,15]. While under-dosing leads to organ rejection overdosing may lead to serious side effects. These side effects include renal toxicity, hypertension, hyperlipidemia, and gastrointestinal complaints with cyclosporine A and tacrolimus [16,17], renal dysfunction, hyperlipidemia, anemia, leukopenia, and thrombocytopenia with sirolimus [18,19], and hyperlipidemia, leukopenia, and thrombocytopenia with everolimus [20]. Therefore, TDM of these immunosuppressants is critical for successful organ transplantation. However, not all immunosuppressants are routinely subjected to TDM because of a wide therapeutic range or a poor correlation between dose and blood levels [7]. For example