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Review

Tacrolimus: An updated review on delivering strategies for multifarious diseases

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ABSTRACT

From the current trends, tacrolimus (TAC) has become an important therapeutic option for the optimal individualization of immunosuppressive therapy especially in case of transplant recipients. TAC is used most frequently in comparison to other immunosuppressants because it offers better safety profile with increased long-term survival in patients especially in children and adolescents. This drug has developed an immense interest in the research field owing to its potential pharmacological scope but due to its poor water solubility, need of concomitant steroids and higher incidences of nephrotoxicity, there comes a need for future research to minimize such limitations and decipher maximum use of the drug. In addition, there are number of formulations attempted to enhance its erratic bioavailability through various techniques namely solid dispersions, inclusion complexes, prodrug approach, SMEDDS *etc.* The present review aims to acknowledge the TAC pharmacokinetic profile and novel drug delivery systems in multiple diseased conditions by particularly enhancing its poor biopharmaceutical issues as well as dose related toxicity. Collectively, we have updated the data pertaining to the drug delivery prospects of TAC for the period of last 8–10 years.

1. Introduction

In US, > 33,500 organ transplants have been carried out till 2016 and when compared with earlier statistics, there have been 20% increase in transplants over 5 years (https://optn.transplant.hrsa.gov/). Organ transplantation as in case of kidney, heart, lung, pancreas, liver, intestinal and hematopoietic stem cell transplantation comprises of a surgical approach in order to substitute a failed or an ailing organ with a healthier donor organ. In spite of global shortage of organs for transplantation, it is one of the most impressive medical achievements of the past decade. Thus, organ and tissue preservation if dealt properly, will benefit millions of patients globally and will change the course of many domains of public health (Giwa et al., 2017). Different approaches are used to test the tissues of an eventual donor along with recipient for compatibility prior organ transplantation (tissue typing or human leukocyte antigen (HLA) typing) (Helderman et al., 1981). The immune system of human body differentiates from its immune functional unit as well as the outside bulk. The phenomenon triggers spurning of transplant by attack on the transplanted tissue or organ through the immune system of recipient only. Humans having immunodeficiency problems are less likely to get prone to organ transplantation rejection. In fact, Miller et al. in 2015 discovered an environment according to which, retention of allograft tolerance governs across the retention of transplant dismissal utilizing the model of mouse cardiac transplantation. According to this study, in the presence of *Listeria monocytogenes* contamination, acute rejection gets triggered and transplantation tolerance gets nullified. Simultaneously, the tolerant state of donor re-emerges, paving a way to the spontaneous acceptance of second transplant (Miller et al., 2015; Yang and Sarwal, 2017). In continuation, drugs inhibiting the immune system (immunosuppressants) are used to prevent the attacking of newly transplanted organs. Immunosuppressants are the active agents causing immunosuppression through drugs or some environmental toxins like polyhalogenated aromatic hydrocarbons, metals, pesticides, aromatic amines, oxidant gases, natural products like selected vitamins, antibiotics, vinca alkaloids, mycotoxins and many more (Council, 1992). Different categories of immunosuppressants are reported according to the pharmacological background, namely, calcineurin (specific T-cell) inhibitors, antiproliferative (cytotoxic) drugs, glucocorticoids and antibodies to suppress rejection of organs (Tripathi, 2009). Calcineurin inhibitors, namely, cyclosporine and tacrolimus (TAC) have been utilized mainly in organ transplantation and their main clinical

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determinants of variability are well known such as food consumption, diarrhoea, haemolytic anemia, hyperlipidaemia, hepatic and kidney disorder and many others (Vanhove et al., 2016a). But TAC is used most commonly in comparison to cyclosporine because TAC gives better safety description along with extended survival among patients but do lacks concerning bioavailability (Boots, 2005; Furlong et al., 2000; Jurewicz, 2003). Surprisingly, TAC has better tolerance in children and adolescents also (Greenbaum et al., 2012; Skeens et al., 2012). According to IMS Health Pharmacy 2010 reports, 48% of adult liver transplant recipients were given TAC, post-transplantation and it tops the list compared to other 15 medications. Surprisingly, the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipient, OPTN/SRTR 2014 Annual Data Report observed that the percentage of recipients procuring mycophenolate mofetil (MMF) along with TAC after 1 year posttransplantation persisted high compared to other regimens followed by 94% TAC users in 2015 (Kim et al., 2017, 2016). The strong reason for prescribing TAC/MMF instead of TAC/AZA or other medications as illustrated through 7-year follow-up can be the beneficial role of MMF in preventing post-transplant diabetes mellitus (Foroncewicz et al., 2013). Apart from this, one case study showed that post heart transplantation, for six years a 23-year old female recipient survived on TAC and MMF, without organ dysfunction simultaneously having successful pregnancy and delivery (Nitta et al., 2016).

Tacrolimus (TAC) or FK506 or Fujimycin, is a lipophilic 23-membered naturally occurring macrolide lactone extracted from *Streptomyces tsukubaensis* with formula weight of 803.5 Da (Fig. 1). TAC has selective inhibitory effect on T-lymphocytes and is a widely used immunosuppressant in organ transplantation. This drug was first described by Tanaka and group in 1990 (Okuhara et al., 1990; Tanaka et al., 1987) and later large number of derivatives, and analogues of TAC were discovered by other groups (Cooper et al., 1989; Grassberger et al., 1989; Honbo et al., 1991; Wallemacq and Reding, 1993). In 2008 Cvak group invented a simple process for the isolation of crystalline TAC from the fermentation broth in a very high yield (Cvak et al., 2008). Going by narrow-therapeutic index (NTI) values of medications, various marketed formulations of TAC have been available under the brand name of Prograf (twice-daily TAC), Advagraf and Envarsus XR (both once-daily TAC formulations) (Garnock-Jones, 2015; Jones-Hughes et al., 2016; Jun et al., 2016; Staatz and Tett, 2015). Current findings based on clinical investigation showed that once-daily prolonged-release TAC (Advagraf®) has led to the improvement in graft survival and minimized costs contradictory to marketed twice-daily immediate release TAC (Prograf®) through base case analysis remarkably in case of liver transplantation (Asrani and O'leary, 2015; Muduma et al., 2016). Fascinatingly, sublingual route has also been discovered which can be considered an alternative option for interim use in subjects who cannot perceive TAC by oral route or through *i.v.* (Gonzales et al., 2016). Studies on lung as well as kidney transplant patients reported that 50% of oral dosage form was required approximately when converted into sublingual administration to achieve therapeutic trough levels (Federico et al., 2016; Pennington and Park, 2015). According to literature, chemistry pertaining metabolism of TAC includes cytochrome P450 3A-mediated hydroxylation, demethylation as well as oxidation.

Subsequent metabolites are classified into two categories: first class involves the derivatives of TAC having alteration at only single place. Second class metabolites are generated by further metabolism of first class and are remodified in more than one position (Fig. 1) (Christians et al., 2002). Pharmacologically, TAC attaches to intracellular FK-binding protein (FK-BP), immunophilin FK506 shaping a complex further inactivating the phosphatase activity of calcineurin. Otherwise, calcineurin when activated encompasses interleukin (IL)-2 transcription by dephosphorylation of nuclear factor of activated T-cells (NF-AT). But the TAC/FK-BP complex or inactivation of calcineurin phosphatase restricts IL-2 production. Further, TAC suppresses the activation and proliferation of T lymphocytes as IL-2 is an autocrine growth factor to it (Fig. 2) (Nasr, 2000).

Tacrolimus is better tolerated and associated with fewer episodes of graft rejection and a reduced need for concomitant steroids. There are other areas where the role of TAC has been discovered and yet to be identified more, namely, ulcerative colitis (Baumgart et al., 2006; Benson et al., 2008; Landy et al., 2013), dermatology (Hossain et al., 2015; Russell, 2002), ophthalmology (Tinwala et al., 2013) and many more use. Based on the animal models of IBD, the drug not just attenuated inflammation but also extraintestinal manifestations. A lot of literature reports as well as clinical data have shown the drug use for the induction of remission in both moderate and severe ulcerative colitis (Fischer and Baumgart, 2017; Matsuhashi et al., 2000; Matsuoka et al., 2015). But, further investigations are required to optimize the use of TAC in such applications especially ulcerative colitis (Matsuoka et al., 2015). Although TAC is not the first-line drug for the treatment of rheumatoid arthritis, it is an effective alternative, mainly when given in combination with methotrexate (Kitahara and Kawai, 2007).

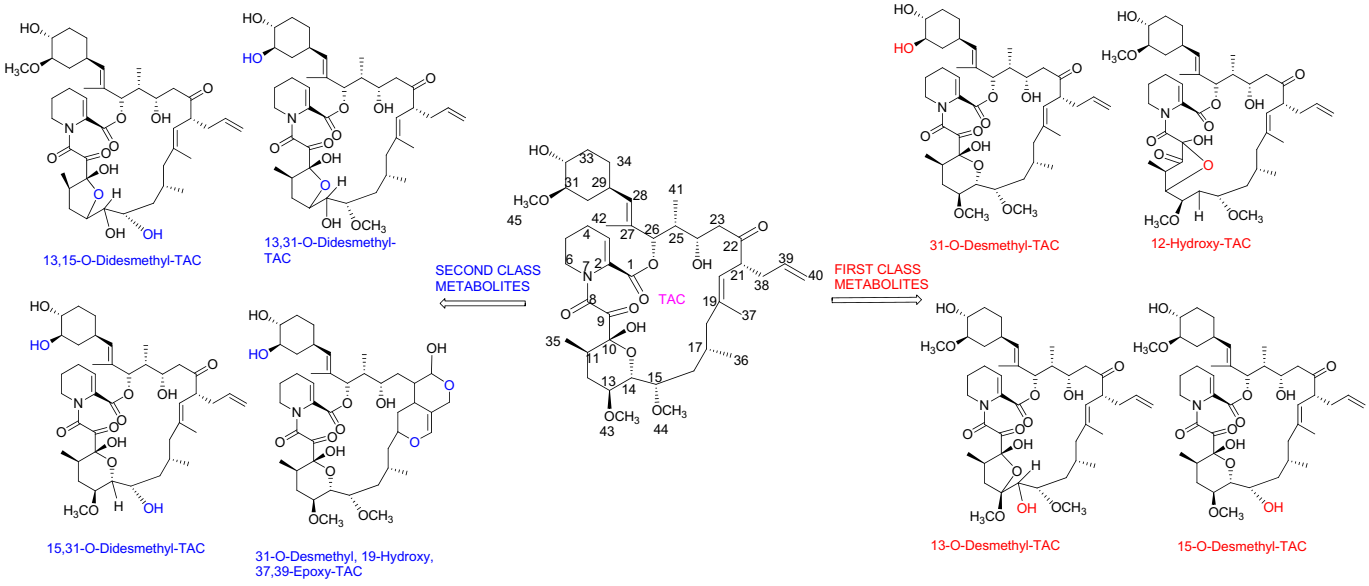

Fig. 1. Chemical structure of tacrolimus (TAC) and its plausible metabolite structures (Christians et al., 2002).

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