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Calcineurin inhibitors in systemic lupus erythematosus

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A B S T R A C T

The calcineurin inhibitors (CNIs) belong to a group of immunosuppressive agents that block T-cell activation through the suppression of the calcium/calcimodulin-dependent phosphatase calcineurin. Agents such as cyclosporine A (CSA) and tacrolimus (TAC) have long been used in patients with systemic lupus erythematosus (SLE). TAC is preferred to CSA in SLE because of the lower frequency of cosmetic, hypertensive and dyslipidemic adverse effects. Recent randomised controlled trials have demonstrated noninferiority of TAC to mycophenolate mofetil (MMF) or cyclophosphamide (CYC) for induction therapy of lupus nephritis. Low-dose combination of TAC and MMF has also been shown to outperform CYC pulses in inducing remission of lupus nephritis in Chinese patients. TAC does not affect fertility and is relatively safe in pregnancy. In SLE patients who are intolerant or refractory to conventional immunosuppressives, or where contraindications to other immunosuppressive agents exist, TAC is an alternative option. However, the therapeutic window of TAC is narrow, and drug level monitoring is required to ensure drug exposure and minimise toxicities. Current evidence of TAC in lupus nephritis is limited to 6 months, and its long-term safety as maintenance therapy of SLE is yet to be determined. Newer chemical analogues of CNIs, such as voclosporin, with less variable plasma concentration are being tested in lupus nephritis.

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Introduction

Systemic lupus erythematosus (SLE) is a complicated multiorgan autoimmune disease that has a predilection for women of childbearing age. The disease course of SLE is highly variable and characterised by periods of flare and remission. Although the pathogenesis of SLE remains enigmatic, multiple pathways contributed by genetic, epigenetic, environmental and hormonal factors in various combinations have been implicated in the development of immunological abnormalities and loss of tolerance to self-antigens [1,2].

A number of immune aberrations have been observed in patients with SLE. These include defective apoptosis and clearance of nuclear autoantigens, nucleosomes and immune complexes by macrophages and the complement system [3]; increased maturation of myeloid dendritic cells, which drive the development of the pro-inflammatory Th17 cells [4]; and defective function of the regulatory T cells (Tregs) and B cells (Bregs) [5,6]. Moreover, clearance of neutrophil extracellular traps, which consist of a rich source of autoantigens, is impaired in patients with SLE [7,8]. Accumulation of apoptotic material and immune complexes stimulates plasmacytoid dendritic cells to produce IFNα and IL-6 through internalisation or interaction with toll-like receptors (TLR7 or TLR9) [9]. The end result of these pathological processes is activation of T helper cells and B cells, which leads to autoantibody production, tissue inflammation and organ injury mediated through various mechanisms.

The calcineurin inhibitors (CNIs) belong to a group of immunosuppressive agents that block T-cell activation through the inhibition of the calcium/calmodulin-dependent phosphatase calcineurin [10]. Agents such as cyclosporine A (CSA) and tacrolimus (TAC) have long been used in organ transplantation. CSA and TAC bind to cyclophilin and FKBP12, respectively, after entry into cytoplasm, suppress calcineurin activity and prevent nuclear translocation of transcription factors such as NF-AT that are involved in IL-2 gene transcription [11]. As a result, T-cell activation is inhibited with a subsequent reduction in the production of cytokines that include TNFα, IL-1β, IFNγ, IL-6 and IL-10; B-cell activation, class-switching and immunoglobulin production are also attenuated [12]. In addition, the CNIs have been shown to exhibit anti-proteinuric effects by stabilising the podocytes in the kidneys [13–15].

A number of open-label prospective or retrospective studies have reported efficacy and glucocorticoid-sparing effects of CNIs in renal and extrarenal manifestations of SLE [16–30]. More recent randomised controlled trials (RCTs) also demonstrated noninferiority of the CNIs to other conventional immunosuppressive agents for induction and maintenance therapy of lupus nephritis [31–38]. Moreover, combination of low-dose TAC and mycophenolate mofetil (MMF) has been shown to be superior to cyclophosphamide (CYC) pulses for inducing remission of lupus nephritis in Chinese patients [39]. In this article, clinical data regarding the use of CNIs in the treatment of renal and extrarenal manifestations of SLE are reviewed.

The pharmacology of CNIs

Both TAC and CSA are highly lipophilic compounds. Because of the low solubility and the extensive first-pass metabolism by the hepatic and gastrointestinal cytochrome P450 isoenzymes and the efflux pump P-glycoprotein (P-gp), the bioavailability of the CNIs is low and variable [40]. Once absorbed from the gastrointestinal tract, the CNIs undergo hepatic metabolism, and the metabolites are predominantly excreted via the biliary tract. Many factors contribute to the pharmacokinetic variability of the CNIs. These include food intake, diarrhoea, intestinal pathologies, anaemia, hypoalbuminaemia, hyperlipidaemia, liver and renal dysfunction, aging, ethnicity, formulation and interaction with concomitant medications that induce or suppress the activity of the cytochrome enzymes [11,40].

The in vitro and in vivo immunosuppressive potency of TAC is 10–100 times higher than that of CSA [41]. In kidney transplantation, RCTs and meta-analysis demonstrated that TAC was more effective than CSA in preventing acute graft rejection and maintaining long-term graft survival [42–44]. Elevated blood pressure, hyperlipidaemia, gingival hyperplasia and hirsutism were also less frequently reported with TAC compared to CSA [45]. As a result, TAC is the preferred CNI for SLE patients.

CSA has been demonstrated to reduce proteinuria through the stabilisation of the actin cytoskeleton in the kidney podocytes [13]. In murine lupus nephritis, TAC ameliorated proteinuria and preserved

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