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Review Article

Efficacy and Cytokine Modulating Effects of Tacrolimus in Systemic Lupus Erythematosus: A Review

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Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease with involvement of both B cells and cytotoxic T lymphocytes and several cytokines aberrations. Standard therapy for SLE has its limitations. Tacrolimus, a novel calcineurin inhibitor with potent immunosuppressive effects, has been shown in the recent years to be effective in SLE therapy. This paper serves to collate the experimental and clinical data on the efficacy of tacrolimus in the treatment of SLE and lupus nephritis. Tacrolimus as a key component of multitarget therapy in SLE is also discussed. The immunocytokine modulatory effects of tacrolimus are also reviewed with reference to SLE. It can be concluded that tacrolimus has an established role in the management of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease with multiorgan involvement characterized by autoantibody formation and immune complex deposition. The pathogenesis of SLE is being unravelled and involves a complex interplay of environmental triggers, hormonal factors, susceptibility genes including genes that control apoptosis rates, antigen/immune complex clearance, lymphoid signaling, and genes that influence inflammatory responses. Examples include lpr gene (Fas mutations) in MRL mice; Clq gene polymorphism; mannose binding lectin gene polymorphism; and IL-10 gene polymorphism [1].

Both B cells and cytotoxic T lymphocytes are involved in the pathogenesis of SLE. The cytokine profile of SLE has been extensively studied. Current theory proposes an overexpression of certain T_H2 cytokines that suppress the T_H1 response in lupus T-cells. Examples include studies in lupus-prone F1 mice showing higher IFN-γ and IL-4 levels and lower active TGF-β levels; and in patients with SLE, serum IL-10 levels were higher than in controls and correlated with disease activity [2, 3].

The standard therapy for SLE includes steroids, antimalarias, azathioprine (AZA), and cytotoxic therapy with cyclophosphamide (CYC). Mycophenolate mofetil (MMF) has been shown to be useful for lupus nephritis and also recently rituximab, anti-B cell therapy has been shown to be efficacious for refractory cases. In this paper, however, I would like to focus on tacrolimus (FK506, Prograf), a relatively new calcineurin inhibitor that has been increasingly used in transplant medicine. Tacrolimus is a macrolide compound isolated from *Streptomyces tsukubaensis*, a soil fungus found in Northern Japan. It was first recognized for its immunosuppressive properties and used extensively in transplantation in the recent years. The objective of this paper is to summarize the reported literature concerning the clinical efficacy of tacrolimus in the management of SLE and the cytokine modulating effects of tacrolimus.

1.1. Tacrolimus in Experimental SLE Models. There were two studies involving MRL/lpr and B/W F1 mice, where tacrolimus was administered to the mice with spontaneous lupus nephritis [4]. The drug was able to reduce proteinuria and prolong the lifespan of the lupus mice and also prevented the progression of the nephropathy. Histopathological study showed that tacrolimus significantly inhibited glomerular hypercellularity and crescent formation. The elevated serum anti-ds DNA was also suppressed by tacrolimus [5].

1.2. Tacrolimus Therapy for SLE without Renal Involvement. Duddridge was the first to report the efficacy of tacrolimus in the treatment of 2 SLE patients with severe cutaneous vasculitis, where cyclophosphamide and cyclosporin had failed [6]. Subsequently, there were some reports of topical tacrolimus being effective for malar rash, chronic discoid lupus, and treatment-resistant cutaneous lupus erythematosus [7–9]. A recent report from Japan also successfully treated 10 SLE patients without renal involvement with tacrolimus [10]. The mean SLE Disease Activity Index (SLEDAI) significantly decreased after 1 year with a reduction of mean dose of prednisolone. The author has also reported 2 patients with SLE with antiphospholipid syndrome who were treated with tacrolimus and had improvement in the manifestations of cutaneous vasculitis and arthritis [11].

1.3. Efficacy of Tacrolimus in SLE with Renal Involvement (Lupus Nephritis). The efficacy of tacrolimus in SLE patients with lupus nephritis was first reported in 4 pediatric patients who had persistent disease activity despite conventional immunosuppressive therapy including AZA, MMF, or CYC [12]. They had marked improvement in disease indices during treatment with FK506.

The author was first to report the therapeutic success of tacrolimus in 6 adult SLE patients with relapsed lupus nephritis [11]. All 6 patients had reduction in proteinuria, having failed conventional immunosuppressive regimes.

Subsequent to these, several reports emerged regarding the usage of tacrolimus in lupus nephritis. An open-labeled pilot study using FK506 as an induction therapy for diffuse proliferative lupus nephritis in 9 patients reported by Mok et al. from Hong Kong showed complete response in 67% and 22% had partial response [13]. This was further confirmed by 2 reports from Zhang et al. where FK506 was found to be comparable to intravenous CYC in the induction therapy of class IV lupus nephritis [14].

Effectiveness of tacrolimus for membranous class V lupus nephritis was also confirmed in case reports and other case series from Japan and Hong Kong [15–17]. As compared with conventional cytotoxic treatment, tacrolimus resulted in a faster resolution of proteinuria, and a lower risk of lupus flare within 1 year.

Recent reports from Japan also showed tacrolimus at 3 mg/day to be effective and safe for maintenance treatment up to one-year follow-up in lupus nephritis [18]. Another double-blind, placebo-controlled study in 63 patients by Nobuyuki et al. also showed that the addition of tacrolimus at 3 mg/day to glucocorticoid therapy resulted in significant improvement in lupus nephritis compared with placebo, up to 28 weeks [19]. This was evident by reduction in the disease activity index, reduction in urinary protein excretion, and increase in complement C3 level.

A novel immunotherapeutic approach has been recently proposed and studied by Bao et al. for the treatment of mixed class V + IV lupus nephritis that is resistant to conventional treatment [20]. Remission rates of this subtype of lupus nephritis are low with only 21% with CTX therapy and 20% with MMF. A six-month study using tacrolimus as induction therapy for this mixed class V + IV lupus nephritis showed a response rate of 21.1% [21]. The new approach of multitarget therapy using a combination of prednisolone, MMF, and tacrolimus showed a significantly much higher complete remission at both 6 and 9 months (50% and 65%, resp.) than with IV CYC (5% and 15%, resp.). In addition, 40% of patients had partial remission at 6 and 9 months follow-up. Adverse events were also less frequent in the multitarget therapy group.

1.4. Cytokine Modulating Effects of Tacrolimus in SLE. The pathogenesis of SLE is complex and involves the FC-receptors system, complements, autoreactive T cells and increased B cell activation, signal pathway alterations, with expansion, hyperreactivity, and production of autoantibodies. A consequence of ongoing T cell stimulation is release of cytokines, and elevation of certain cytokines in SLE has been well recognized, especially during periods of clinical activity. The "lupus storm" of hyperpyrexia and vascular collapse seen more in the presteroid era of SLE might also have had a component of a cytokine release syndrome [22].

Interferon-α (IFN-α) was the first cytokine found to be elevated in SLE and increased levels correlated with disease activity. High levels of tumour necrosis factor alpha (TNF-α) have also been identified in some patients with active SLE and positively correlate with levels of circulating autoantibodies. Serum IL-6 and IL-10 are also increased in SLE patients [23].

In SLE, it appears that both the T_H1 and T_H2 responses are in operation. A T_H1 environment favours the production of autoimmunity that is characterized by T cell mechanisms, while autoimmunity involving antibody formation is fostered by a T_H2 environment. T_H1 cells characteristically produce IL-2, IFN-γ, IL-12, and TNF-α, while T_H2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13.

Tacrolimus binds to FK-binding proteins (FKBPs) in the cytoplasm, and the complex associates with the calcium-dependent calcineurin/calmodulin complexes to impede calcium-dependent signal transduction in lymphocytes [24]. This causes the transcription factors that promote cytokine gene activation to be reduced.

In terms of the cytokine modulating effects of tacrolimus, it potently inhibits T cell activation-induced TNF-α and IL-1β production in vitro by human peripheral blood mononuclear cells (PBMCs) [25]. Tacrolimus was also found to be more potent than dexamethasone and cyclosporin A in that regards. The cytokine suppressive effects of tacrolimus have been studied in various autoimmune conditions. Both T_H1 (IL-2, IFN-γ) and T_H2 cytokines (IL-4, IL-5) were found to be suppressed by tacrolimus in atopic dermatitis [26]. In the rat adjuvant-induced arthritis model, FK506 was found to be more effective than methotrexate in reducing elevated levels of inflammatory cytokines, TNF-α, IL-1β, and IL-6 [27]. The suppression of IL-6 production and IgM production by FK506 was also confirmed in human PBMC [28]. This is important in SLE therapy as IL-6 overexpression induces B cell differentiation and increases production of autoantibodies. In the myasthenia gravis model, where PBMCs of patients were cultured for cytokine profile and studied, the culture study showed reduced IL-12, IL-17, IFN-γ, GM-CSF, TNF-α,

and MIP-1β in patients who received tacrolimus [29]. This suggests that tacrolimus inhibits T cells and macrophages and enhances type 1 regulatory T cells. A recent study also confirmed that treatment with tacrolimus inhibited the expression of T_H1 cytokine mRNA in lupus-prone mice [30].

In addition, tacrolimus has been shown to inhibit IL-10 production [31]. This is important as IL-10 plays an important role in the pathogenesis of SLE [32]. The deleterious effects of IL-10 include stimulation of terminal B cell differentiation, activation induced cell death, and a suppressive effect on T cell. Elevated levels of IL-10 are seen in SLE patients and correlated with SLE activity.

In terms of affecting the humoral immunity response, tacrolimus does not target B cells directly but works indirectly by interfering with T cell help [33]. Tacrolimus decreased the expression of the costimulating ligands (CD154 and CD278), reducing the ability of T cells to activate B cells. Tacrolimus also attenuated B cell stimulatory cytokine mRNA levels in T cells, thereby abrogating B cell signals necessary for activation and class-switching. Hence, tacrolimus is able to inhibit T-cell-dependent immunoglobulin production.

The ability of tacrolimus to affect T cells is important in the immunotherapeutic strategy of SLE treatment. Cytotoxic T lymphocytes is an important effector pathway in the pathogenesis of SLE. CD8+ T lymphocytes are activated by SLE dendritic cells into effector-type cytotoxic T lymphocytes, and an increased proportion of cytotoxic T lymphocytes correlated with SLEDAI scores [34]. A recent study found predominance of CD8+ T lymphocytes among periglomerular-infiltrating cells in the renal biopsy specimens of patients with class III/IV lupus nephritis [35]. Using immunochemistry studies, renal CD8+ T cell infiltration correlated with the renal activity index and high serum creatinine levels. There were also correlations with cellular crescents and Bowman's capsule rupture, and association with a poor response after conventional induction therapy.

This understanding may explain why the multitarget therapy for the treatment of class V + IV lupus nephritis was highly effective with 90% achieving complete and partial remission compared with 45% with IV CYC therapy. The effect of tacrolimus on T cells may be a critical component of the observed benefits in the study by Bao et al. [20] as the severe focal and segmental forms of lupus nephritis have a dominant T cell-dependent pathogenesis [36]. MMF, besides suppressing lymphocyte proliferation and decreasing antibodies formation, can suppress IL-2 production additionally when given with tacrolimus [37]. Hence, multitarget therapy using a combination of MMF, tacrolimus, and steroids, previously shown to be an effective treatment for early mixed cellular and humoral renal allograft rejections in the field of organ transplantation, can now be applied to the therapy of severe or resistant SLE, particularly lupus nephritis.

2. Conclusion

Having reviewed the experimental and clinical evidence available to date on the efficacy of tacrolimus in the treatment of SLE, it can be concluded that tacrolimus has an established role in SLE management. Immunocytokine studies support the clinical efficacy of tacrolimus through direct T cell suppression, inhibiting B cell activity indirectly by interfering with T helper signals and cytokine suppression including T_H1 cytokines, IL-2, IL-6, and IL-10.

Based on current available evidence, I would recommend the usage of tacrolimus in SLE management as follows:

(1) as a steroid sparing agent;

(2) effective in SLE without renal involvement;

(3) effective in SLE with renal involvement;

  (a) in class IV lupus nephritis,
  (b) in class V lupus nephritis,
  (c) in class V + IV lupus nephritis (as multitarget therapy),

(4) as an induction therapy, maintenance therapy and also in relapsed cases as a disease remitting agent.

The use of multitarget therapy needs to be further studied and even extrapolated to the management of severe SLE patients with other organ involvements. Tacrolimus is a useful and efficacious addition to the armamentarium of SLE immunotherapy.

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