The New Choice of Tacrolimus in the Treatment of Refractory Ulcerative Colitis

Abstract

Recent studies have found that a new immuno-suppressant of tacrolimus (Tacrolimus, FK506) has the effect of inducing remission and maintaining therapy in the treatment of Ulcerative Colitis. Its mechanism may be correlated with the inhibition of T cells and related cytokines. This mini review will summarize the anti-inflammatory mechanisms of tacrolimus and provide a brief overview of several up to date clinical studies on tacrolimus in UC treatment.

Keywords: Ulcerative Colitis; Tacrolimus; Mechanism; Clinical Trails

Abbreviations: UC: Ulcerative Colitis; NFAT: Nuclear Transcription Factor; IEC: Intestinal Epithelial Cells; G-CSF: Granulocyte Colony Stimulating Factor; FKBP12: FK506-Binding Protein

Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory bowel disease with lesion confined to the colonic mucosa and sub mucosa [1]. According to the activity degree, UC can be clinically classified as mild, moderate and severe refractory diseases. Aminosaliclylates and corticosteroids are traditional medicines used for mild and moderate UC, respectively, while immuno-suppressants (e.g., methotrexate and cyclosporine A) are generally used for severe refractory UC [2,3]. Unfortunately, approximately 30% of UC patients eventually require surgery after treating with these traditional medicines, which are mainly due to their gastrointestinal reaction, renal toxicity and neurotoxicity [4]. Therefore, there is an urgent need to develop a novel medicine to improve the outcomes in patients with UC. Tacrolimus that targets a specific immunological pathway has been studied as a promising UC therapeutics [5,6]. This review will provide a brief overview of several up to date clinical studies on tacrolimus in UC treatment.

Tacrolimus (FK506) is a macrolide immuno-suppressant isolated from fermentation broth of Streptomyces tsukubaensis [7] (Figure 1). The target cells of tacrolimus are similar to cyclosporine A, a calcineurin inhibitor. Cyclosporine A has been demonstrated to be effective in the remission of severe refractory UC. However, cyclosporine A tends to be associated with a higher incidence of significant hypertension, hyperlipidaemia, hirsutism, gingivitis, and gum hyperplasia, thus its potential toxicity limits its usage in clinic [8]. In contrast, tacrolimus has a lower incidence of hypertension and hypercholesterolemia than cyclosporine A, and is rarely associated with the cyclosporine A specific adverse effects, such as hirsutism, gum hyperplasia and gingivitis [9]. In addition, numerous studies have shown that the immuno-suppressive activity of tacrolimus on lymphocyte was 10-100 times higher than cyclosporine A [10]. Therefore, tacrolimus has been considered as a promising alternate of cyclosporine A to treat severe refractory UC.

In general, UC is considered as the dys-regulation of the immune system [11]. Dys-regulation of the immune system induces an abnormal immune response including the over-production of adhesion molecules, and abnormal activation of T cells [12]. It is known that tacrolimus has a strong immune inhibition and anti-inflammatory effect by inhibiting the proliferation of T cells. The inhibition mediated process occurs when tacrolimus enters cells and combines to the immunophilin FK506 binding protein 12 (FKBP12), thus forms FK506-binding protein complex (FK506BP12). This complex makes calcium phosphatase inactive, therefore inhibits the translocation of the transcription factor of activated T cells that promote IL-2 mediated proliferation of helper T cells [13] (Figure 2). In addition, tacrolimus will suppress the expression and release of G-CSF and interleukin by intestinal epithelial cells and NKT cells [14]. The increased levels of G-CSF and interleukin are associated with mucosal inflammation. These cytokines continue to drive the inflammatory response, leading to ongoing inflammation [15]. All the above possible mechanisms explain the promising benefits of tacrolimus in UC treatment. However, more research is warranted to confirm the clinical consequences of tacrolimus.

The clinical trial of tacrolimus in UC was initially investigated in several small randomized studies. In a study conducted by Fellermann et al. [16], a total of 11 patients with severe refractory UC were treated with intravenous tacrolimus for 7-10 days followed by oral treatment for 7 months. In this study, 64% of patients achieved clinical remission, and surgery was even avoided in 81% of patients. Moreover, corticosteroids tapering achieved in four patients. In another study on patients with severe refractory UC, the successful treatment rate of tacrolimus was achieved to 67% at two weeks [17]. In a subsequent retrospective study, a total of 38 patients received oral tacrolimus. The results showed clinical remission and response rates were 44% and 52%, respectively [18]. Furthermore, Kasugai et al.
[19] reported cytokine levels in refractory UC patients before and after administration of tacrolimus. It turned out that serum IL-8 and G-CSF levels were 20.6 and 6.8 pg/mL before treatment, and 9.0 and 2.0 pg/mL after 12 weeks of treatment, respectively (p=0.05). Therefore, the treatment with tacrolimus reduced serum IL-8 and G-CSF levels in UC patients, which was associated with an overall reduction in disease severity. This confirmed the mechanism of action of tacrolimus via inhibiting cytokines pathway.

Based on the promising results from the previous studies, a randomized, double blind placebo controlled study was initiated to evaluate the efficacy of tacrolimus as induction and maintenance therapy in UC. This study involved 62 moderate-severe UC patients with intolerance to intravenous corticosteroids. The patients were divided into placebo and tacrolimus groups with an initial oral dose of 0.10-0.15 mg/kg aiming for a serum drug target trough levels of 10-15 ng/mL. The results showed that the patients receiving tacrolimus had a statistically greater clinical remission rate, clinical response and mucosal healing at week 2, when compared to the placebo group. Specifically, there were 50% induction of clinical response, 9.4% induction of clinical remission, and 43.8% mucosal healing in the tacrolimus group. In contrast, in the placebo group there were 13.3% induction of clinical response (p=0.003), 0.0% induction of clinical remission (p=0.298), and 13.3% mucosal healing (p=0.012). In addition, open-label extension phase of the study was well tolerated, with only minor side effects and no patients required colectomy [20].

In a subsequent trial the efficacy of tacrolimus as maintenance therapy was evaluated. In a retrospective analysis of 44 patients (with intolerance or no responders to traditional medicines) treated with tacrolimus at multiple research centers, clinical remission and mucosal healing rates were achieved to 65.9% and 43.8% at 12 weeks, respectively, and 84.1% of the patients avoided colectomy at 51.7 weeks [21]. In another study, Landy reported that the response and remission rates at 6 months were 52% and 44%, respectively, and 68% of patients avoided colectomy at 17 months [22]. Recently, a large retrospective survey of the efficacy and safety of tacrolimus in German UC patients was reported [23]. After tacrolimus treatment, 130 moderate-severe UC patients showed a clinical remission rate of 72% at 12 weeks. It should be noted that the most common adverse events of tacrolimus were finger tremor and urinary infections. Moreover, in a large retrospective analysis the tolerability of tacrolimus was evaluated. Gilles reported that treatment-emergent adverse events associated with tacrolimus included finger tremor, diarrhoea, urinary infections, gastrointestinal disturbance and nephrotoxicity. All others adverse events were mild and tolerated. In the group of patients treated with tacrolimus the adverse events rate was 46%. The most serious adverse events found in this group were severe allergic reactions, leading to tacrolimus discontinuation. Virtually all patients receiving tacrolimus experienced at least one treatment-emergent adverse event. Many adverse events are dose dependent and respond to dosage reduction. However, no lethal or severe adverse events occurred, indicating that tacrolimus was safe and tolerable [24,25].
Conclusion

The aforementioned clinical trials have shown that tacrolimus is effective in short-term remission of severe refractory UC and is able to avoid colectomy for patients with no response to traditional medicines. Moreover, although corticosteroids suppress active inflammation in the acute setting, the long-term use of them will lead to unacceptable toxicity and high relapse rates [26]. Compared to corticosteroids, tacrolimus seems to be better tolerated in long-term use. Therefore, tacrolimus serves as a potential alternative option for severe refractory UC treatment prior to conventional medicines, including aminosalicylates, corticosteroids and immuno-suppressants.

References