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Review

Tacrolimus use in lupus nephritis: A systematic review and meta-analysis

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ABSTRACT

There is growing interest in the role of tacrolimus as a potential therapeutic agent in SLE. This systematic review and meta-analysis evaluates the evidence for tacrolimus use in the management of lupus nephritis.

Thirteen controlled studies were identified (9 suitable for inclusion), using Cochrane database, SCOPUS, Web of Science and OVID (MEDLINE and EMBASE). Data on complete and partial remission rates, proteinuria reduction and adverse events was extracted and analysed using RevMan software.

The meta-analysis showed that overall tacrolimus is more effective at inducing complete renal remission than IVCYC ($p = 0.004$), but there is no significant difference compared to MMF ($p = 0.87$). Multi-target TAC + MMF therapy is more effective than IVCYC only when partial remission is included ($p = 0.0006$). Frequency of key adverse effects seems comparable to other agents used in the management of lupus nephritis with fewer gastrointestinal side effects, leukopenia, menstrual disorders, infections and episodes of liver dysfunction reported, but more new onset hypertension and hyperglycaemia. Mortality was lower in the tacrolimus groups, but this was not statistically significant ($p = 0.15$). Tacrolimus may be more effective at reducing proteinuria, but again this was not statistically significant. There are no controlled trials looking at use in pregnancy or juvenile patients, however case reports suggest potential efficacy and safety.

In conclusion, in moderately severe lupus nephritis, there is some evidence supporting efficacy of tacrolimus or multi-target TAC + MMF over IVCYC, but no evidence supporting tacrolimus over MMF. Tacrolimus may be more effective at reducing proteinuria, having potential implications for long-term outcome. Key limitations of this study are the lack of long-term outcome data and the lack of high quality, large, blinded controlled trials in multi-ethnic groups.

Contents

Abbreviations: SLE, Systemic Lupus Erythematosus; TAC, tacrolimus; MMF, mycophenolate mofetil; IVCYC, intravenous cyclophosphamide; AZA, azathioprine.

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1. Introduction

Lupus nephritis is one of the most serious and common complications of systemic lupus erythematosus (SLE), especially in non-Caucasian patients, with Chinese patients having a 60% cumulative incidence of renal disease at 5 year post-diagnosis [1]. Current treatments are associated with significant adverse effects, therapy failure and relapse rates, so there is an ongoing search for more effective, less toxic options.

Where renal biopsy shows pure mesangial involvement (class I or II), this has a better prognosis and may require only renin-angiotensin-aldosterone inhibition. Low-dose glucocorticoids, occasionally in combination with immunosuppressive agents may be required for extra-renal lupus manifestations [2]. However, this review focuses on more severe membranous, proliferative or membranoproliferative lupus nephritis (Class III, IV, V or combination) [3].

Treatment and prognosis have advanced greatly in recent decades with the first breakthrough occurring in the late 1970s when it was reported that the addition of cyclophosphamide to the standard corticosteroid-only regimen showed reduced relapse rates in diffuse proliferative lupus nephritis [4,5]. The so-called NIH regimen was widely adopted and recommended monthly, 'pulsed' intravenous cyclophosphamide (IVCYC) (0.5-1 g/m^2) for 6 months, extended quarterly for up to 2 years. However adverse effects were common with high rates of sepsis, amenorrhea, haemorrhagic cystitis and malignancy [6]. The subsequent Euro-Lupus Nephritis Trial showed low dose IVCYC (6 fortnightly pulses at 500 mg each) followed by azathioprine (AZA) to be equally effective at inducing renal remission and reducing flares, but with a trend towards fewer infections [7].

Since the mid-1990s, induction therapy with mycophenolate mofetil (MMF) has emerged as a useful alternative which was found to be equally or more effective, and safer than monthly IVCYC [8]. Hydroxychloroquine is another valuable immunomodulatory agent with established safety that was shown to prevent disease flares in a randomised withdrawal trial [9].

Most modern regimens are based around current 2012 EULAR/ERA-EDTA guidelines, favouring hydroxychloroquine for all patients with lupus nephritis, as well as corticosteroids with either MMF or low dose IVCYC (total 3 g over 3 months) for the induction treatment of lupus nephritis class III or IV. Higher dose IVCYC is reserved for those with adverse histological or clinical prognostic factors. In pure class V nephritis with nephrotic range proteinuria MMF is recommended. Cyclophosphamide, calcineurin inhibitors or rituximab are used as alternatives in non-responders. Subsequent maintenance therapy is then recommended as either MMF or AZA, with low-dose glucocorticoid for at least 3 years, or calcineurin inhibitors in pure class V nephritis [2].

The evidence for choice of maintenance therapy is from the double-blinded ALMS trial that reported superior efficacy and safety with MMF versus AZA.[10] Conversely, the smaller, open-labelled MAINTAIN trial did not detect a difference [11]. Nevertheless, both MMF and AZA were associated with very low rates of doubling of serum creatinine, end-stage renal disease and death. AZA remains a useful option, especially if other drugs are contra-indicated (e.g. during pregnancy) or not tolerated.

There may be a role for rituximab in the management of lupus nephritis, however the LUNAR trial failed to show improved remission rates with adjunctive rituximab compared to placebo given concomitantly with MMF and corticosteroids [12]. Larger randomised-trials with longer follow-up and comparing rituximab directly to other therapies are needed. The ongoing RITUXILUP trial aims to assess whether the combination of rituximab, MMF and no oral steroids is as effective as MMF and oral steroids in treating lupus nephritis [13].

Following encouraging results in randomised controlled trials, there is increasing interest in whether tacrolimus (previously known as FK506) could have a more prominent role in the management of lupus nephritis. It is a T-cell specific calcineurin inhibitor first discovered in a soil sample from Mount Tsukuba in Japan. It already has a long history of use in renal transplantation and the mechanism of action is therefore well described. Tacrolimus forms a complex with immunophilin FK506 binding protein 12, which then inhibits the phosphatase activity of calcineurin, resulting in a reduction of IL-2 transcription and activation of T cells [14]. Production of IL-2, IL-4, IL-5, IFN-γ and TNF-α are all decreased [15]. Animal studies have shown it to delay onset and progression of renal disease in MRL/lpr lupus-prone mice [16,17].

Cyclosporin A is another calcineurin inhibitor, although pharmacological studies have calculated tacrolimus to be approximately 25 times more potent [18]. A previous meta-analysis has found better remission rates with calcineurin inhibitors compared to IVCYC, with tacrolimus favourable to cyclosporin A [19]. Other recent meta-analyses have found similar rates of remission between IVCYC, MMF and tacrolimus with the available evidence to that point [20,21]. This systematic review aims to include the most recently published studies, using only controlled studies, and also looks more broadly at tacrolimus use in pregnancy and paediatrics.

2. Methods

On 17th June 2015 the Cochrane database, SCOPUS, Web of Science and OVID (EMBASE and MEDLINE) search engines were searched for the keyword terms "lupus nephritis" and "tacrolimus or FK506". Only articles written in English were included and no date restrictions were applied. All controlled prospective or retrospective trials relating to patients with a diagnosis of SLE complicated by lupus nephritis were eligible for inclusion.

To indicate research quality, for each of the randomized controlled trials, the Jadad score was calculated, considering randomization, blinding procedures and the provision of an accurate account of all included patients [22]. For cohort studies the Newcastle-Ottawa scoring system was used, with stars awarded for meeting specific criteria regarding patient selection procedures, comparability of cohorts and methods of outcome assessment [23].

To improve comparability between studies, 6-month data was used where available. Due to variation in the nature of the intervention and control groups, the complete and partial remission data has been analysed separately for three different groups:

a) Multi-target TAC and MMF versus IVCYC
b) TAC versus IVCYC
c) TAC versus MMF.

Secondary outcomes were not reported in all studies and therefore due to the overall small number of studies, all studies were pooled together to compare tacrolimus arms (including TAC + MMF), to control arms (IVCYC, MMF or Placebo).

The meta-analysis was performed using Revman 5.3 software [24]. The Mantel-Haenszel method was used with a 95% confidence interval. Heterogeneity was measured using the I^2 index and where this was greater than 0.01 a random effects model was used to compensate for this. Where I^2 was less than 0.01 a fixed effect model was used.

3. Results

After exact duplicates were removed 570 potential papers were identified. This was reduced by excluding papers clearly about other topics, single case reports, meta-analyses or review articles, narrowing the number of papers of interest to 68. These were scrutinized in more detail to identify 11 randomized controlled trials and 2 controlled cohort studies. Of these 13 articles, 3 were excluded as they demonstrated preliminary or subgroup analysis data of other included studies. One was excluded as it was a follow up study of subjects who had already achieved remission from an earlier included study. Fig. 1 summarises this process. As no controlled trials were found regarding tacrolimus use in pregnancy or paediatric onset lupus nephritis, prospective and retrospective cohort studies on these subtopics were also considered.