# Benefit/risk of cyclosporine in rheumatoid arthritis

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**ABSTRACT**

*Combination therapy has emerged as a crucial therapeutic tool to control aggressive rheumatoid arthritis (RA). Cyclosporine (CsA) when combined with methotrexate (MTX) has shown substantial benefit in clinical practice. The primary benefit is its positive effect in the control of joint-bone erosions. The most feared adverse effect is the development of nephrotoxicity, which may be in part hemodynamic and in part structural, i.e. fibrotic. Careful monitoring of concomitant drugs, hypertension and through blood levels should allow the patient to maintain normal renal function. The successful employment of CsA in lupus nephritis clearly supports this statement.*

## Introduction

In the era of biological (anti-TNF) therapy for rheumatoid arthritis (RA), we could ask ourselves what might be an appropriate place for cyclosporine A (CsA) in the treatment of this disease. It is believed that T cells are crucial in the early and later stages of synovitis and for the persistence of inflammation, together with macrophages (1, 2). This constituted the rationale for the use of CsA in RA, the effects of which on T lymphocytes have been extensively studied (3, 4). More recent studies have highlighted the inhibitory action of CsA on other proinflammatory cells, including neutrophils (5) and antigen presenting cells (APC) (6).

## Actions of cyclosporine A

CsA inhibits T cell activation by interfering with calcium-dependent signalling events involved in lymphokine gene transcription. Once it enters a cell, CsA binds to cyclophilin and this complex competitively inhibits the enzymatic activity of calcineurin, a serine/threonine phosphatase required for the dephosphorylation of nuclear factor for activated T cells (NF-AT) and activated protein-1 (AP-1) (7). This blockade prevents NF-AT and AP-1 translocation into the nucleus and results in the failure to initiate the transcription of several T-cell cytokine genes, such as IL-2 (8), IL-3, IL-4, tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony stimulating factor (GM-CSF), and interferon-γ (IFN-γ) (9, 10). The result is inhibition of T-cell activation and suppression of T-cell dependent immune responses. CsA also appears to have additional actions.

Several studies have suggested the importance of another cytokine, IL-17, in the complex cytokine network that regulates bone destruction and inflammation in RA (11-13). IL-17, which is produced by CD4+ CD45RO+ memory T cells (14) of the rheumatoid synovium, also induces synoviocytes to produce IL-6, IL-8, GM-CSF and prostaglandin E2 (PGE2), a major mediator of inflammation, and monocytes/macrophages to produce TNF-α, IL-1 and nitric oxid (NO) (16), and stimulates osteoclastogenesis, increasing the expression of the receptor activator of the nuclear factor κB ligand (RANKL) (12,15). Ziolkowska *et al*. (17) has shown that IL-15, a critical cytokine contributing to the pathogenesis of RA (18,19), but not TNF-α, induces the production of IL-17. Thus IL-15–triggered IL-17 secretion is completely or partially blocked in the presence of low doses of CsA, suggesting a further pathway of action of CsA and a possible rationale for combination therapy with anti TNF–α drugs.

CsA also interferes with the inducible degradation of NF-κB inhibitors (20), leading to a decrease in NF-κB transcripting effects, which is also important for IL-15 gene activation.

Cho and collaborators (21) evaluated the effect of CsA on rheumatoid synovial fibroblasts (FLS) and found that CsA increases the production of NF-κB and of IL-10, an antagonist of Th1 and proinflammatory cytokines (22, 23), and decreases IL-15 and TNF–α transcription in the FLS through a cAMP–dependent pathway.

Another mechanism of action of CsA is the up-regulation of the expression and synthesis by T cells and macrophages of transforming growth factor–beta 1 (TGF-β1), a cytokine with immunosuppressive effects that is able to down-regulate Th1 cells toward Th2 function and to switch off antigen-presenting cells (24).

In RA affected joints, chronic inflammation is also maintained by neovascularization, required to transport inflammatory cells and oxygen to the hyperplastic synovial membrane. Among the numerous angiogenic factors, several studies (25, 26) have demonstrated that RA angiogenesis is associated with enhanced expression of vascular endothelial growth factor (VEGF), a potent endothelial cell mitogen. Hernandez *et al.* demonstrated *in vitro* and i*n vivo* that CsA inhibits the migration of primary endothelial cells and the angiogenesis induced by VEGF; this effect appears to be mediated through the CsA-dependent inhibition of cyclooxygenase 2 (Cox-2), a gene induced by VEGF via NF-AT activation (27). Another study (28) showed that CsA, by down-regulating AP-1, inhibits both constitutive and TGFb-induced VEGF production by rheumatoid synovial fibroblasts. These findings suggest an antiangiogenic property of CsA and thus an additional positive effect on disease activity.

**The benefits of cyclosporine A – Clinical studies**

Clinicians began to study CsA for the treatment of RA in 1980, after the observation of a therapeutic effect in some psoriatic patients (29). In the first studies in RA patients, CsA was generally used as a "rescue therapy" in patients who were non-responders to other common DMARDs and in monotherapy. The other general features in these trials were that patients had long-standing disease at entry with poor prognostic factors and several previous failed drugs, and CsA was administered at high doses (ranging between 5 and 10 mg/Kg/day). Overall these open (30-34), as well as controlled or randomized studies (35-39), initially evaluating small groups of patients, indicated clinical efficacy but also a great number of adverse events.

Subsequent clinical studies performed in patients with early RA using lower doses of CsA demonstrated good control over clinical and radiologic progression. Pasero and colleagues (40), in a prospective randomised trial with a blind radiologic endpoint, obtained similar clinical results when treating patients with cyclosporine (mean dose 3 mg/Kg/day) or other common DMARDs, but the CsA group showed a significant delay in erosion progression, with acceptable tolerability. Zeidler *et al*. (41) in an 18-month randomized study obtained similar results in slowing radiologic progression of joint damage with CsA and parenteral gold, when the analysis was performed on an intention-to-treat basis. After analyzing only the valid compliant completers, the CsA group showed significantly lower disease progression and better tolerability. In fact, more "gold" patients than "CsA" patients withdrew from the study because of adverse events, even though renal damage was seen with CsA in an extension study at 3 years (42).

Drosos and collaborators (43) compared CsA with methotrexate in early RA patients in a 42-month prospective study, and found substantial clinical improvement, no serious side effects and no radiographic progression in about 70% of patients in each group (at 3 1/2 years of follow-up). These findings could suggest the importance of an early pharmacologic intervention, as well as the use of effective and safe drugs, to prevent articular damage and to preserve function.

According to these clinical trial data, CsA monotherapy shows at least similar efficacy to the other conventional DMARDs. However, in practice monotherapy cannot properly control disease activity in most patients. Moreover, radiological progression may be observed, although it is slower than that seen with placebo.

These findings led to the use of combination therapy in several clinical trials, with additive efficacy when cyclosporine (50) was combined with methotrexate (MTX), antimalarial agents or gold salts (44-49, 53).

Due to the need to initiate treatment as soon as possible in the disease course to assure optimal results, aggressive therapeutic approaches were attempted in two recent studies. The first study employed an aggressive regimen at onset with two or more DMARDs ("step-down" approach), the second began with one DMARD and added a second in patients with an incomplete response ("step-up" approach). Marchesoni *et al*. (51) treated 57 patients suffering from early and non-erosive arthritis with a combination of CsA and MTX for 6 months, obtaining a good ACR response, and then randomised the patients to receive CsA or MTX alone. After 24 months, 72% of CsA patients have discontinued the study, mainly because of loss of efficacy, compared to a drop-out rate of 14% among those taking MTX. Both groups showed progression in radiographic erosion scores.

In the study of Proudman and colleagues (52), aggressive therapy with MTX, CsA and intra-articular corticosteroids was introduced at onset in early RA with a poor prognosis. This combination led to a faster response but not to a significant improvement in the outcome compared with sulfasalazine (SSZ) monotherapy. The authors concluded that another – e.g. step-up – approach is needed.

The step-up approach was used by Ferraccioli *et al*. (54), who reported the results of a 3-year prospective study in early RA patients who were treated initially with MTX or CsA or SSZ monotherapy, followed by step-up combination therapy with two or three drugs in cases of poor response. More than 70% of patients receiving combination therapy obtained the primary end-point of an American College of Rheumatology criteria 50% response (ACR 50) at the 18-month follow-up with tolerable side effects.

Hochberg and collaborators (55), in a literature review of randomised placebo-controlled trials, analysed the results of step-up strategy therapy in patients who showed an incomplete response to MTX, and found no significant differences in the achievement of ACR 20 criteria with the addition of

cyclosporine, etanercept, infliximab or leflunomide. These conclusions could be limited by the use of the ACR 20 response, which may not be sensitive enough to differentiate between two or more active drugs. Two recent reviews documented that cyclosporin A has similar efficacy to other DMARDs, including anti-TNF agents, in slowing radiographic progression (56, 57).

Little is known about combination therapy with anti-TNF, other than with MTX, although a possible additive therapeutic effect in association with CsA has been demonstrated in collagen-induced arthritis in rats (58). Temekonidis *et al.* (59) treated with infliximab a series of 18 severe refractory RA patients who were receiving low dose CsA (2 mg/Kg/day) and could not tolerate MTX, with a satisfactory response and good tolerability.

The potential benefit of CsA as a steroid-sparing drug and in inducing partial or complete remission in Still's disease, a condition with an extensive inflammatory response characterized by high levels of IL-6 and IFN–γ, has also been documented (60-62).

**Table I.** Adverse events associated with cyclosporine (63).

| Adverse events | Relative frequency (%) | Withdrawal frequency (%) |
|---|---|---|
| More serious | | |
| Abnormal renal function | 20-30[a] | 1% |
| Irreversible renal damage | < 1[b] | – |
| Hypertension | 10[c] | < 1 |
| Infection | < 1[d,e] | < 1 |
| Less serious | | |
| Hypertrichosis | 15-20 | < 1 |
| Diarrhea | 3-5 | < 1 |
| Nausea | 5-10 | 1 |
| Headache | 5-10 | < 1 |
| Paresthesia | 5-10 | < 1 |
| Tremor | 3-5 | < 1 |
| Edema | 3-5 | < 1 |
| Hypomagnesemia | < 1 | – |

[a] Associated with starting renal function, age and dose of CsA.
[b] Rare with proper dosage adjustment.
[c] More frequent with underlying hypertension.
[d] With lower CsA doses seen primarily in patients taking concomitant cytotoxic therapy.
[e] < 1% = rare occurrence.

**Table II.** Factors implicated in CsA nephrotoxicity.

| Acute nephrotoxicity | Ref. | Chronic nephrotoxicity | Ref. |
|---|---|---|---|
| Endothelin (↑) | 69, 70 | Endothelin (↑) | 69, 70 |
| Angiotensin II (↑) | 67, 68 | Angiotensin II (↑) | 81 |
| Nitric oxide (↓) | 73 | Nitric oxide (↓) | 73 |
| Prostaglandin (↓) | 71, 72 | Aldosterone (↑) | 83 |
| Leukotrienes (↑) | 100 | TGF-β (↑) | 78 |
| Sympathetic system (↑) | 74 | Macrophage infiltration (↑) | 84 |
| Free radicals (↑) | 66 | Osteopontin (↑) | 84 |
| Adenosine | " | COX-2 (↓) | 72 |
| Vasopressin (↑) | " | VEGF (↓) | 66 |
| Platelet activation factor (↑) | " | Metalloproteinase (↓) | " |
| Atrial natriuretic factor | " | TIMP (↑) | " |
| Kallikrein-kinin system | " | | |
| Cholesterol (↑) | " | | |
| Hypomagnesemia | " | | |
| Extracellular volume depletion | " | | |
| Direct tubular epithelial cell toxicity | " | | |

## Risk of cyclosporine A – The pathogenesis of nephrotoxicity

CsA therapy is associated with a series of side effects (Table I), most of which are reversible with an adjustment of the dose. The most significant adverse effect is acute or chronic nephrotoxicity. Acute CsA nephrotoxicity takes the form of functional damage without permanent structural injury, which reverses when the CsA is reduced or discontinued. Acute nephrotoxicity is linked to a renal imbalance in the vasoconstrictor and vasodilator mediators, causing intra-renal vasoconstriction (mainly in the afferent arterioles) and a decrease in the renal blood flow (RBF) and impairment of the glomerular filtration rate (GFR) (64, 65). There is evidence that a large number of mediators are implicated in functional renal damage since only partial improvement is seen with treatments targeting these mediators; the pathogenesis of CsA-induced vasoconstriction is multi-factorial and not entirely understood (66) (Table II). Several studies point to a role of CsA in the activation of the renin-angiotensin-aldosterone system (67, 68), the enhanced release of endothelin-1 (a potent vasoconstrictor) by renal epithelial cells (69, 70), an imbalance in the ratio of the vasodilator prostacyclin and the vasoconstrictor thromboxane A2 (in animal models CsA also suppresses the expression of renal cyclooxygenase-2) (71, 72), impairment of endothelium-dependent vasodilatation mediated by nitric oxide (73), and activation of the sympathetic system (74).

Chronic CsA-induced nephropathy is characterized by an irreversible striped interstitial fibrosis, tubular atrophy with the accumulation of focal inflammatory cells, and degenerative hyaline changes in the afferent arteriole walls (even if recent studies found evidence that arteriolopathy, but not tubulointerstitial changes, are reversible after discontinuing CsA) (75-77). The development of chronic CsA damage is complex and mediated by several factors.

One of the most important cytokines implicated in the pathogenesis of renal fibrosis is TGF-b, which acts by stimulating extracellular matrix deposition in the mesangium and reducing collagenase expression (78). However, not all studies confirmed that the administration of anti-TGF-β antibodies could completely prevent renal damage (79, 80), thus suggesting the role of other factors. Indeed, there is evidence that angiotensin II activates fibroblasts and induces extracellular matrix deposition (81), an effect blocked by enalapril (82). In rats, aldosterone-blockade (spironolactone) prevents the decrease in renal function and the up-regulation of TGF-β (83).

Table II presents a series of the possible factors involved in CsA nephrotoxicity.

**Risks of side effects – Clinical studies**

It is well documented that irreversible renal histological lesions can appear in transplant patients after just six months of high dose CsA therapy (85) with possible progression over time even after CsA dose reduction (86). There is less unanimity regarding the long-term nephrotoxic effects of the low-dose regimens used in autoimmune diseases. Several clinical studies have evaluated the correlation between CsA therapy, impairment of renal function and histologic findings. In the International Kidney Biopsy Registry of Cyclosporin (Sandimmune) in Autoimmune Diseases, CsA abnormalities were found in 4 of 41 patients who had received a maximum CsA dose of 4.6 mg/Kg/day for 16 months; none of 11 renal biopsies taken from RA patients who did not undergo CsA therapy showed these abnormalities (87). Sund *et al.* (88) reported findings consistent with CsA-induced nephropathy in 4 out of 10 renal specimens in RA patients treated with < 5 mg/Kg/day of CsA for about 40 months.

In a long-term follow-up of cyclosporine therapy, biopsies were performed on 60 RA patients who were given CsA for a mean of 19 months and a second biopsy was taken in 14 patients after 39 months of CsA therapy (89). CsA-related morphologic changes were noted in 5 of 60 patients at the first biopsy and in one further patient at the second biopsy. Nephropathy was not seen in patients whose initial cyclosporine dosage was less than 4 mg/Kg/day and who subsequently received doses no higher than 5 mg/Kg/day. Abnormalities in renal function were reversible on discontinuation or reduction of CsA. The conclusion that low-dose cyclosporin results in a low risk of developing renal damage was reached also by Landewe and colleagues, who found a similar incidence of renal structure abnormalities in 11 RA patients treated with a mean CsA dosage of 4.4 mg/Kg/day (with a decrease in creatinine clearance of 26%) and in 22 RA patients with previous gold or D-penicillamine therapy (90).

Vercauteren and collaborators (91) performed a meta-analysis of the literature on CsA-induced nephrotoxicity in autoimmune diseases. They selected 18 controlled, randomised reports published between 1986 and 1995, eleven of which were conducted in RA patients, three in psoriasis, three in Crohn's disease and one in uveitis. In these trials the CsA dosage was < 10 mg/Kg/day (mean 4.8 mg/Kg/day) and dose adjustment was performed if serum creatinine increased by more than 30% to 50%. All the studies reported a statistically significant rise in serum creatinine level for CsA-treated patients compared with their baseline value and with a control group. The weighted percentage increase in serum creatinine level of all studies was 17% in the CsA-treated group (852 patients) compared to 1.7% in the control group (763 patients). Thirteen of the selected papers reported a reversibility of the renal impairment, even if in seven among these the reversibility was only partial (five studies did not mention any follow-up results). The authors conclude that the administration of CsA in patients with autoimmune diseases implies a certain (definite) risk of nephrotoxicity and that a rigorous evaluation of the risk-benefit ratio is necessary for each patient with a careful follow-up (92). However, to date there is an agreement that the strict application of the well established guidelines for safe CsA use can prevent irreversible loss of renal function (93-95, 96-99).

Moreover, CsA was used successfully in the treatment of lupus nephritis (a condition which itself causes renal function impairment, leading to a rise in serum creatinine and chronic renal histopathologic lesions) with no significant alterations in serum creatinine. A repeat renal biopsy in some of these SLE patients after CsA therapy did not show CsA-related toxicity findings (101-106).

**Conclusion**

CsA was the first drug that helped the rheumatologists to understand the true role of T cells in the rheumatoid inflammation. Monotherapy with CsA is of limited benefit, but combination therapy with CsA and methotrexate represents one of the best options to control aggressive disease. In these cases it could represent a real options prior to TNF blockers. More than ten years of experience have clearly documented that the actual risk of nephrotoxicity is limited when guidelines are strictly followed. Good results in lupus nephritis provide support for this conclusion.

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