

# Multidisciplinary Focus on Cyclosporin A

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**ABSTRACT.** Cyclosporin A (CsA) has been proved to be effective in the treatment of severe cutaneous psoriasis and psoriatic arthritis (PsA). In psoriasis, CsA therapy can be used as: (1) intermittent short-course therapy; (2) continuous longterm therapy; (3) crisis intervention; and (4) a combination of sequential and rotational therapy. Several open prospective studies have shown the short-term efficacy of CsA in PsA. While there were no randomized controlled trials (RCT) comparing CsA to placebo, 3 published controlled trials compared CsA to other disease modifying antirheumatic drugs (DMARD). These studies support the efficacy of CsA in patients with PsA and peripheral arthritis. However, no conclusions can be drawn on the efficacy of CsA for dactylitis and axial disease. Longterm studies have shown the persistent efficacy and safety of CsA in PsA. The beneficial effects of CsA in angiogenesis-related diseases such as PsA and cutaneous psoriasis may also be mediated by its ability to block the angiogenic effects induced by vascular endothelial growth factor. (J Rheumatol 2009;36 Suppl 83:52-55; doi:10.3899/jrheum.090225)

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Cyclosporin A (CsA) has been proved to be effective in the treatment of severe cutaneous psoriasis and psoriatic arthritis (PsA). In psoriasis, CsA therapy can be used as (1) intermittent short course therapy; (2) continuous longterm therapy; (3) crisis intervention; and (4) a combination of sequential and rotational therapy<sup>1-3</sup>. CsA is recommended at an initial dose of 2.5 mg/kg/day; however, a higher induction dose of 3–5 mg/kg/day may be required if the psoriasis is particularly active.

Intermittent short course CsA therapy (< 12–16 weeks) is effective and safe in many patients with severe psoriasis. A 12–16 week course of CsA at a dose of 2.5–5 mg/kg/day provided a rapid improvement or complete clearance of disease in 80%–90% of patients<sup>4,5</sup>. Intermittent short course CsA therapy has minimal renal toxicity and hypertensive effect.

Longterm continuous CsA therapy is required for maintaining a sustained disease remission in a minority of patients with recalcitrant disease. The majority of patients can be maintained on a CsA dose < 3.5 mg/kg/day<sup>6,7</sup>. However, careful control of renal function and blood pressure is mandatory in these patients for the increased risk of nephrotoxicity and hypertension.

Short-term treatment (4–8 weeks) with CsA may be used as crisis intervention for the rapid onset of action of CsA in reducing an acute flare or treating severe forms of psoriasis<sup>8</sup>. Short-term treatment with CsA may also restore responsiveness of disease to usual treatments.

Combination or rotational therapies using CsA tend to minimize toxicity and optimize efficacy. Several agents including fumarates, sulfasalazine, mycophenolate mofetil, and biological agents have been added to rotational therapy cycles with CsA.

During the 1980s, some studies evaluating the use of CsA in severe cases of psoriasis inadequately controlled by traditional therapy documented an improvement in both psoriasis and its associated articular manifestations. Subsequently, several open prospective studies showed the short-term efficacy of CsA in PsA<sup>9-11</sup>. Kavanaugh, *et al*, on behalf of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), performed an evidence based systematic review of treatments for PsA<sup>12</sup>. While there were no randomized controlled trials (RCT) comparing CsA to placebo, 3 published controlled trials compared CsA to other disease modifying antirheumatic drugs (DMARD)<sup>13-15</sup>. The evidence supports the efficacy of CsA in patients with PsA and peripheral arthritis (level 1b–3, grade B). However, no conclusions can be drawn on the efficacy of CsA for dactylitis and axial disease.

This review will mainly focus on CsA therapy for PsA.

## MECHANISM OF ACTION OF CYCLOSPORIN A

CsA is an immunosuppressive drug that inhibits the activity of transcription factors of the nuclear factor of activated T cell family, interfering with the induction of cytokines and other inducible genes required for the immune response. In stimulated T cells, CsA inhibits activation principally by suppressing interleukin 2 (IL-2) production and IL-2 receptor (R) expression<sup>16</sup>.

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Inhibition of IL-2 production blocks the activation of T helper cells, T regulatory cells (autocrine loop), natural killer cells, and monocytes. In addition, Hernandez, *et al* found that CsA inhibits migration of primary endothelial cells and angiogenesis induced by vascular endothelial growth factor (VEGF). This effect is mediated through the inhibition of cyclooxygenase-2, the transcription of which is activated by VEGF in primary endothelial cells<sup>17</sup>.

Reece, *et al* examined the macroscopic vascular pattern of early knee synovitis in PsA and rheumatoid arthritis (RA). A distinct vascular pattern was observed to distinguish between PsA and RA, with tortuous, bushy vessels in the former and predominantly straight, branching vessels in the latter<sup>18</sup>. Angiogenesis is under control of growth factors (transforming growth factor- $\beta$  and VEGF) that may play an important role in the increased vascular pattern observed macroscopically and histologically in PsA. Fearon, *et al* showed a significantly increased expression of VEGF in the blood vessels of synovial membrane in early PsA compared to early RA synovial membrane<sup>19</sup>. Further, serum VEGF levels at presentation were found to be elevated in patients with early PsA (< 2 years from onset)<sup>20</sup>. Therefore, the beneficial effects of CsA in angiogenesis-related diseases such as PsA and cutaneous psoriasis may also be mediated by its ability to block the angiogenic effects induced by VEGF.

Only a few studies have evaluated the *in vivo* effects of CsA on serum immunologic variables in patients with PsA. The normalization of the reduced percentage of some lymphocyte subpopulations was observed in PsA patients during a 6-month course of CsA treatment<sup>21</sup>. In a second study, CsA treatment was not able to change serum RANTES levels that were higher in patients with PsA than in a control population<sup>22</sup>. However, PsA patients with persistently normal RANTES levels had a better response to CsA treatment. An Italian study showed that CsA significantly reduced the levels of sIL-2R in the PsA patients who responded to treatment<sup>23</sup>. The authors observed a parallel decrease in joint pain/tenderness score and serum sIL-2R values. Finally, in a pivotal study, Macchioni, *et al* showed that a normal serum sIL-2R level after 6 months of therapy had a prognostic value for a good outcome in patients with PsA treated with CsA<sup>24</sup>.

## RANDOMIZED CONTROLLED TRIALS

In the first prospective controlled, randomized trial, 35 patients with PsA were enrolled<sup>13</sup>. The efficacy and toxicity of CsA (3–5 mg/kg/day) versus methotrexate (MTX; 7.5–15 mg weekly) over a period of 1 year were evaluated. After 6 and 12 months the numbers of painful and swollen joints, Ritchie index, duration of morning stiffness, patient and physician global assessments, and

the Psoriasis Area and Severity Index (PASI) were significantly improved in both treatment groups. CsA and MTX were equally effective treatments for PsA, but the withdrawal rate after 1 year was more frequent in the CsA arm (41% vs 28%), although the difference was not statistically significant.

An Italian 24-week RCT compared the efficacy and tolerability of CsA (3 mg/kg/day) with that of symptomatic therapy (ST) alone (nonsteroidal antiinflammatory drugs, analgesics, and/or prednisone < 5 mg/day) and sulfasalazine (SSZ; 2 g/day)<sup>15</sup>. In comparison with both SSZ and ST, there was a statistically significant difference in favor of CsA in terms of the mean changes in the pain score, which was considered the primary response variable. A significant decrease in favor of CsA versus ST alone was also observed for swollen joint count, tender joint count, joint/pain tenderness score, patient and physician global assessments by at least 1 point, total Arthritis Impact Measurement Scale score, and spondylitis functional index. There was a statistically significant difference in the American College of Rheumatology (ACR) 50% and ACR 70% response rates between the CsA and ST groups. Comparing the SSZ and ST alone groups, only the spondylitis functional index decreased significantly in the SSZ treated patients. The PASI was significantly lower in the CsA versus the ST and SSZ groups. Decrease in erythrocyte sedimentation rate was significant only in the SSZ versus the ST group, whereas reduction in C-reactive protein (CRP) was significant in the CsA treated patients compared with the ST group. The most common adverse event in the CsA group was mild, reversible kidney dysfunction. This open trial showed that CsA is well tolerated by patients with PsA and it is more efficacious than ST or SSZ.

In a 12 month, randomized, double blind, placebo controlled trial, 72 patients with active PsA with an incomplete response to MTX monotherapy were randomized to receive either CsA (n = 38) or placebo (n = 34)<sup>14</sup>. In the active but not in the placebo arm there were significant improvements in swollen joint count and CRP values as compared with baseline. The PASI score improved in the active group as compared with placebo. Synovitis detected by high resolution ultrasound was significantly reduced by 33% in the active group compared with 6% in the placebo group. Therefore, combination therapy of MTX with CsA may be useful in PsA patients demonstrating an incomplete response to MTX monotherapy.

## LONGTERM EFFICACY AND EFFECT ON RADIOLOGICAL PROGRESSION

A 2-year prospective, nonrandomized study showed the persistent efficacy of CsA in controlling disease activity in patients with PsA. Forty nine patients completed the

2-year treatment period. After 6 months the numbers of painful and swollen joints, Ritchie index, duration of morning stiffness, patient and physician global assessments, the Health Assessment Questionnaire, and the PASI were significantly improved. Further, clinical responses were not different between 12 months and 24 months of treatment, indicating that the clinical response remained stable over the 2 years of followup<sup>25</sup>.

An Italian study evaluated the radiological progression of joint damage in patients with PsA treated with CsA and possible clinical and/or immunological variables that might predict outcome<sup>24</sup>. Twenty-four patients with active disease entered a 2-year open prospective study on CsA (starting dose 3 mg/kg/day). Fifteen patients completed the study. Plain radiographs of hands and feet at study entry and at the end of followup were compared for number of eroded joints. sIL-2R levels were available in 13/15 patients before CsA therapy, after 6 months, and after 2 years. The mean number of eroded joints per patient increased significantly during the study period. Nine patients had less than 2 new eroded joints (responders), while the remaining 6 patients had 5 or more new eroded joints (nonresponders). Serum sIL-2R levels were in the normal range after 6 months and 2 years of CsA treatment in all the responder patients and were above the 95th percentile of the control population in the 6 nonresponders. The conclusions of this study were that (1) CsA seems to control 2-year progression of the radiological damage in peripheral joints in 60% of PsA patients; and (2) normal serum sIL-2R level after 6 months of therapy seems to have a prognostic value for a good outcome in PsA patients treated with CsA.

## SAFETY

An Italian study reviewed the toxicity of CsA in the treatment of patients with PsA<sup>11</sup>. Of the 170 CsA-treated PsA patients in 16 studies, only 16 (9.4%) suspended the drug because of side effects. The most important side effect was nephrotoxicity (10 of 170: 6%); the other 6 patients discontinued CsA because of uncontrolled hypertension (4 patients) and gastrointestinal discomfort (2 patients). However, most of the described side effects were mild or transient and did not require termination of CsA. The conclusion of this review was that CsA seems to be a safe therapy for PsA.

Potential irreversible nephrotoxicity is a major concern with longterm use of CsA. Further, patients with PsA, who are often also treated with nonsteroidal anti-inflammatory drugs, may be more sensitive to the renal effects of CsA. The risk of renal damage is known to be related to the CsA dose and to the maximum increase in serum creatinine<sup>26,27</sup>. The strategies used in RA, such as the careful selection of patients, a low CsA dose of 2.5–4 mg/kg/day using the microemulsion formulation, and a reduction in dose to limit any increase in

serum creatinine to less than 30% of baseline levels, have efficiently minimized CsA-induced nephrotoxicity<sup>26,27</sup>. Renal biopsies of 60 patients with RA treated for a period of 87 months showed that pathological findings consistent with CsA-induced nephropathy were surprisingly rare<sup>28</sup>. None of the 22 patients who had received < 4 mg/kg/day as a starting dose showed any pathological changes or signs of functional deterioration. The longterm use of CsA in RA showed that survival on treatment was better in the CsA group than in the DMARD control group after 3 years<sup>29</sup>. Sarzi-Puttini, et al have also confirmed the longterm safety of CsA in PsA patients<sup>25</sup>. During the 2-year study period, CsA therapy was stopped in only one patient because of raised serum creatinine levels, which were resistant to a reduction in CsA dosage.

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