Revisiting Cyclosporine in the Age of Biologics: Update on Efficacy and Mechanism of Action

Increased understanding of the immunologic basis of psoriasis supports the role of cyclosporine in patient management.

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Our understanding of the immunological basis of psoriasis and the ability to treat this disease with immunosuppressants has greatly expanded in the past few decades. With respect to the pathogenesis of psoriasis, the entire refocusing from keratinocyte hyperproliferation to immunology started with the serendipitous discovery that immune modulating agents, namely cyclosporine, led to undeniable and often dramatic psoriasis improvement with no effect on keratinocyte reproduction.1,2 Eventually, understanding the role of immunology in psoriasis combined with new knowledge of protein engineering techniques has given us the capability to manufacture specific proteins that selectively alter the immunologic processes in psoriasis, leading to the advent of biologics. However, of the immunosuppressive agents, cyclosporine remains one of the most efficacious agents available for the treatment of psoriasis.

Cyclosporine was first extracted in 1969 from the fungus Tolypocladium inflatum Gams and in 1976 Borel reported immunosuppressive properties of cyclosporine in animal models.3,4 Three years later, cyclosporine A was used experimentally in transplant patients to prevent graft rejection, and it was in these trials that Muller reported improvement of lesions in transplant patients who happened to have psoriasis.2 Following this discovery, further research led to a preliminary understanding of the mechanism of action of cyclosporine.

Cyclosporine permeates into target cells and binds to molecules known as the cyclophilins. This

**Take-Home Tips.** The use of older systemic agents, such as cyclosporine, has fallen out of the limelight. Unlike newer agents, cyclosporine produces a broad “upstream” anti-inflammatory effect on the immune pathogenesis of psoriasis by blocking the activation of Th1 cells, Th17 cells, and TIP-dendritic cells. This leads to very good efficacy and wider applicability in not only dermatology but also many other medical specialties. Therefore, the merits of cyclosporine should be re-evaluated in the age of biologics.
cyclosporine-cyclophilin complex binds calcineurin (a calcium-dependent serine/threonine phosphatase), preventing nuclear factor of activated T cell (NFAT) dephosphorylation and thereby inactivating the transcription factor NFAT.\(^5,7\) Because NFAT dephosphorylation is essential for transcription of a number of cytokine genes, including IL-2, IL-4, IFN-\(\gamma\), and TNF-\(\alpha\), the “upstream” prevention of NFAT dephosphorylation suppresses the transcription of these cytokines and inhibits activation of various T cells, B cells, and macrophages.\(^8\) (Figure 1)

Because of the central role of IL-2 in the process of naïve T-cell clonal expansion and mature T-cell activation, many earlier studies with cyclosporine focused on its suppression of this specific cytokine\(^5\) (Figure 2). Impairment of IL-2 production by cyclosporine has been clearly demonstrated in human, murine, feline, and guinea pig models.\(^5,9-11\) In addition, earlier studies have also shown that treatment with cyclosporine at low doses (2.5mg/kg or 5mg/kg) markedly reduced the number of cells expressing IL-2 receptor, thereby revealing another method by which it may downregulate T-cell activation.\(^12\) However, newer findings have demonstrated an even broader effect on the inflammatory immune pathogenesis. This review article provides an update on cyclosporine’s effect on the immune system and reviews its role in the treatment of an entire spectrum of immune mediated skin diseases.

Studies to Date
We performed a literature search for in vitro studies, in vivo studies, clinical trials, randomized control trials, and review articles between 1984 and 2010. The key word cyclosporine was combined with mechanism of action, immunology, cytokines, and molecular biology. We then searched for other off-label uses of cyclosporine. The search yielded over 65 articles, of which 51 were chosen for this review. The pertinent data are reviewed here.

Originally, psoriasis was thought to be mediated mainly by the activation of Th1 cells. However, new discoveries have revealed the importance of a new T-cell subtype, Th17, in the development of autoimmune diseases including psoriasis. Th17 cells are activated by the dendritic cell cytokine IL-23. They produce IL-17, IL-22, and TNF, and have many other downstream pro-inflammatory effects (Figure 2). Haider et al. profiled affected genes in skin biopsies of psoriasis patients receiving cyclosporine 4mg/kg/day.\(^13\) Greater than 95 percent of CSA- down regulated genes were associated with pro-inflammatory cells and skin resident cells such as keratinocytes and fibroblasts. Within two weeks of commencing treatment with cyclosporine, there was a strong inhibition of two pathways. First, Th1-type T cell activation was suppressed by decreased STAT1, IFN-\(\gamma\), and several downstream genes regulated by IFN-\(\gamma\) such as genes for IL-12 and IL-4. Second, there was suppression of Th17 activation with decreased IL-17, IL-22, and down regulated downstream genes including DEFB-
2, LCN-2, CXCL1, and CCL20. Hence, this study suggests that the effects of cyclosporine on the immune system go well beyond the suppression of IL-2 and the Th1 mediated pathway, but also suppress the Th17 pathway.13

Interestingly, the authors of this same study also detected a significant suppression of dendritic cell genes during cyclosporine treatment.14 Dendritic cells were strongly reduced, with decreased CD83 cell surface protein expression as well as multiple gene products associated with dendritic cell maturation. More specifically, cyclosporine suppressed key inflammatory products of TNF/iNOS producing dendritic cells (TIP-DC), a newly recognized population of inflammatory dendritic cells in psoriasis. These CD11c+ myeloid-derived dendritic cells produce pro-inflammatory cytokines including IL-20, IL-23, TNF, and iNOS (inducible nitric oxide synthase) and activate epidermal keratinocytes.15 In psoriasis, cyclosporine decreased genomic expression of IL-23, TNF, and iNOS. In fact, the genes of the TIP-DC pathway correlated best with disease remission when the entire treatment period was considered.13

Lastly, the authors note no effects of cyclosporine on gene expression in the blood in contrast to the above findings from skin biopsies. Hence, although there was a strong inhibition of pro-inflammatory cytokines in the skin, this was not correlated with suppression of these cytokines in peripheral circulation.

Discussion
With the advent of new, targeted agents for the treatment of psoriasis, the focus on older immunosuppressant agents such as cyclosporine has diminished. However, clinical study results suggest cyclosporine to be higher in efficacy than many of the biologic agents. In a randomized, double blind study by Koo in 1998, 309 patients with severe, chronic plaque-type psoriasis were randomized to receive either Neoral (Novartis) or Sandimmune (Novartis) starting at a mean dose of 2.5mg/kg/day for 24 weeks with dose escalation as needed after four weeks of treatment. By week 12, 80.3 percent of patients in the Neoral group (n=152) and 78.2 percent in the Sandimmune group (n=157) achieved PASI-75. No average dose was reported, but 90 percent of patients attaining PASI 75 were able to do so at a dose of less than 3.5mg/kg/day.16

The results from most clinical trials with the biologics reveal lower efficacy results than cyclosporine. In a study with alfacept (Amevive, Astellas), 21 percent of patients achieved PASI 75 at week 14 with a dose of 15mg/week for 12 weeks.17 Etanercept (Enbrel, Amgen/Pfizer) in a phase III trial for 12 weeks showed PASI-75 in 49 percent of patients when used 50mg twice weekly and 34 percent when used 25mg twice weekly.18 In another pivotal phase III study, 67.7 percent of patients at week 12 treated with the currently approved dosing for adalimumab (Humira, Abbott) achieved PASI-75.19 In a phase III,
randomized, double blind study, 80 percent of patients receiving infliximab (Remicade, Centocor Ortho Biotech, Inc.) 5mg/kg at weeks 0, 2, and 6 achieved PASI 75 at week 10.20 The newest biologic agent, ustekinumab (Stelara, Centocor Ortho Biotech, Inc.), in one phase III trial showed PASI 75 response at week 12 in 67.1 percent of patients receiving the 45mg dose and in 66.4 percent of patients receiving the 90mg dose.21 Another larger phase III trial with the same agent showed PASI 75 in 66.7 percent of patients receiving 45mg and 75.5 percent of patients receiving 90mg.22 Hence, among newer biologic agents, only infliximab (80 percent) has reached the reported efficacy of moderate dose cyclosporine (80.3 percent) (Figure 3).

Cyclosporine’s effective immunosuppressive action is also evidenced by its treatment of a wide range of immune mediated diseases. An extensive literature search revealed effective treatment with cyclosporine in over 50 different disease processes.23-44 (Table 1) Of note, in addition to psoriasis, there are 32 other dermatologic uses of cyclosporine including severe atopic dermatitis,36 pyoderma gangrenosum,36 refractory lichen planus,37 and many bullous skin disorders.28 On the other hand, the use of biologic agents is currently limited to only a few diseases, including rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, and juvenile idiopathic arthritis in addition to psoriasis and psoriatic arthritis. Successful dermatologic off-label uses for biologics have been similarly limited to hidradenitis suppurativa, Hailey-Hailey disease, pyoderma gangrenosum, systemic lupus erythematosus, and Behcet’s disease.45,46

From the new immunological findings presented above, this superior efficacy and wider clinical applicability may be explained by the broader effect of cyclosporine on the immune pathogenesis. Unlike the targeted biologic agents that inhibit only one or, at most, two specific cytokines, cyclosporine leads to the down-regulation of multiple immune mediators (Figure 4). In addition, its strong inhibition of IL-2 and down-regulation of IL-2 receptor gene transcription leads to an “upstream” blockade of the immune cascade in contrast to TNF inhibitors that produce a more “downstream” blockade. Lastly, cyclosporine appears to affect the activation of the three major players in the immunology of psoriasis—Th1 cells, Th17 cells, and TIP dendritic cells—in contrast to biologic agents that block only the products of these cells. This, for cyclosporine, produces a broader effect on the immune system and a subsequent superior clinical response compared to the relatively focused action of the biologic agents.

**Conclusion**

The biologics have taken the center stage for psoriasis treatment in the past few years. With this, the use of...
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