Cyclosporine and psoriasis: 2008 National Psoriasis Foundation* Consensus Conference

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Background: Cyclosporine is a valuable option for the treatment of psoriasis. This report summarizes studies regarding the use of cyclosporine since the last guidelines were published in 1998.

Objective: A task force of the National Psoriasis Foundation Medical Board was convened to evaluate treatment options. Our aim was to achieve a consensus on new updated guidelines for the use of cyclosporine in the treatment of psoriasis.

Methods: Reports in the literature were reviewed regarding cyclosporine therapy.

Limitations: There are few evidence-based studies on the treatment of psoriasis with cyclosporine.

Results: A consensus was achieved on the use of cyclosporine in psoriasis including specific recommendations on dosing, monitoring, and use of cyclosporine in special situations. The consensus received approval from members of the National Psoriasis Foundation Medical Board.

Conclusions: Cyclosporine is a safe and effective drug for the treatment of psoriasis. It has a particularly useful role in managing psoriatic crises, treating psoriasis unresponsive to other modalities, bridging to other therapies, and treating psoriasis within a rotational scheme of other medications. Appropriate patient selection and monitoring will significantly decrease the risks of side effects. (J Am Acad Dermatol 2010;62:838-53.)

Key words: cyclosporine; psoriasis; psoriatic arthritis; review; therapy.

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Funding sources: None.

Disclosure: Dr Gottlieb served on the advisory board of and was a speaker and consultant for Amgen Inc and Wyeth Pharmaceuticals; has consulting/advisory board agreements with Beiersdorf, Abbott, Sankyo, Kemia, Actelion, Novo Nordisk, Immune Control, Dermipsor, Can-Fite, Celgene, Centocor Inc, Bristol Myers Squibb, Warne Chilcott, Roche, Medarex, Celera, UCB, Almirall, RxClinical, Medacorp, and Incyte; and has consulted for Magen, PureTech, and Teva. She received grants from Amgen, Wyeth Pharmaceuticals, Immune Control, Celgene, Centocor Inc, Incyte, and Pharmacare. Almost all income has been paid to her employer directly. Dr Lebwohl served on the advisory board of and was speaker for Abbott Labs, Amgen, Astellas, Centocor, Galderma, Genentech, Stiefel, and Warner Chilcott, receiving honoraria; served on the advisory board of and was consultant and speaker for PharmaDerm, receiving honoraria; was speaker for Novartis and Ranbaxy, receiving honoraria; was consultant for Biogen, UCB, DermiPsor, Isotechnika, Sanofi-Aventis, Triax, and York Pharma, receiving honoraria; and served on the advisory board of Medicis and Pfizer, receiving honoraria. Members of Dr Lebwohl's department own patents on short-contact tazarotene, topical genistein, and use of the excimer laser for vitiligo. Dr Elewski was an investigator receiving grants from Abbott, Amgen, Centocor, Ortho Neutrogenia, and Stiefel; was a consultant receiving honoraria from Intendis and NanoBio; and was a consultant and investigator receiving honoraria and grants from Schering Plough. Dr Elewski's department received compensation that does not benefit her directly from Amgen, Novartis, Mediquest, Astellas, Abbott, Barrier, and Centocor. Dr Rosmarin disclosed no relevant conflicts of interest.

Reprints not available from the authors.

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Published online November 25, 2009.
0190-9622/$36.00

doi:10.1016/j.jaad.2009.05.017

There has been an impressive increase in the number of therapeutic options for psoriasis in the past decade.[1] However, since its therapeutic effects were discovered in 1979, cyclosporine remains an invaluable agent in the treatment of psoriasis.[2] Cyclosporine's original formulation (Sandimmune) was approved in 1983 for the prevention of organ rejection and the more bioavailable microemulsion formulation (Neoral) was approved in 1997 for the treatment of psoriasis and rheumatoid arthritis. Cyclosporine has also been used off-label in a diverse range of dermatologic conditions.

Although there have been past guidelines,[3,4] this article presents available data to achieve a consensus on new updated guidelines for the use of cyclosporine in the treatment of psoriasis. It was reviewed and approved by members of the National Psoriasis Foundation Medical Board. To minimize the toxicity of any therapy, proper patient selection and appropriate monitoring are crucial. The decision to administer cyclosporine should be individualized. Each patient should be evaluated with reference to disease severity, quality of life, and general medical and psychologic status.

CAPSULE SUMMARY

- Cyclosporine is a T-cell inhibitor and is very effective in rapidly treating different types of psoriasis.
- Patients on cyclosporine need to be carefully monitored for nephrotoxicity, hypertension, and other side effects.
- Because cyclosporine is metabolized by the cytochrome P450 3A4 system, there are important drug interactions.
- Special considerations need to be taken for patients taking cyclosporine if they are under 18, pregnant, have hepatitis C, or are on other psoriasis treatments.

MECHANISM OF ACTION OF CYCLOSPORINE

Cyclosporine primarily acts by inhibiting T-cell function and interleukin (IL)-2.[5] In psoriatic skin, after an antigen-presenting cell binds to a T cell, intracytoplasmic levels of calcium increase, leading to calmodulin activation of calcineurin phosphatase. Calcineurin phosphatase dephosphorylates nuclear factor of activated T cells, which allows translocation of the protein into the nucleus where it enables transcription of proinflammatory genes including IL-2, IL-4, interferon-gamma, transforming growth factor-beta, and up-regulation of the IL-2 receptor. Cyclosporine freely diffuses into the cytoplasm of T cells, complexes with cyclophilin, which binds and inhibits calcineurin phosphatase leading to lower levels of dephosphorylated nuclear factor of activated T cells. Reduced levels of nuclear factor of activated T cells lead to lower levels of inflammatory cytokines, thus inhibiting T-cell activation.[6,7] Cyclosporine down-regulation of intercellular adhesion molecule-1 on keratinocytes and endothelial cells prevents the recruitment of inflammatory cells into the skin.[8] Cyclosporine also has an effect on dendritic cells and in reducing Th17 pathway genes, decreasing levels of tumor necrosis factor (TNF), inducible nitric oxide synthase, as well as IL-23p19, IL-17, and IL-22.[9] Another possible mechanism of cyclosporine includes decreasing vascular endothelial growth factor, an angiogenic factor involved in the pathogenesis of psoriasis.[10]

EFFICACY OF CYCLOSPORINE IN PSORIASIS

There are numerous clinical trials proving the efficacy of cyclosporine in plaque-type psoriasis in both inducing remission and in maintenance therapy.[11] Cyclosporine at doses of 2.5 to 5 mg/kg/d for a 12- to 16-week period produces rapid and significant improvement in psoriasis in 80% to 90% of patients.[12-16] At 3 mg/kg/d, Psoriasis Area and Severity Index (PASI) 75 is achieved in 50% to 70% of patients and PASI 90 in 30% to 50% of patients.[17] Cyclosporine is also effective in treating pustular,[18] erythrodermic,[19] and nail[20] psoriasis.

There are a few studies contrasting cyclosporine to other psoriasis treatments. In a trial comparing 210 patients on either cyclosporine or etretinate, the mean PASI score improvement was 71% in the cyclosporine group and 47% in the etretinate group.[21] In a randomized controlled trial comparing 88 patients on either cyclosporine or methotrexate, after 16 weeks, the improvement in PASI 75 in the two groups was similar: 71% for cyclosporine and 60% for methotrexate.[22] In a randomized controlled trial of 84 patients with moderate to severe plaque psoriasis, after 12 weeks, the mean PASI score change was 72% in the cyclosporine group and 58% in the methotrexate group.[23]

Short-course therapy with cyclosporine can lead to intermediate-term disease control and sustained remission in some patients. The PISCES group[14,15] examined 400 patients in an open, multicenter, randomized trial of intermittent short courses of cyclosporine either tapered or abruptly stopped in control of psoriasis for 1 year. Patients were randomized to two groups: abruptly discontinued