applied twice per day as a placebo control.[10]

When calcipotriol is combined with phototherapy, it is important to make sure that the patient does not apply calcipotriol within two hours before phototherapy because otherwise, some patients experience a burning sensation, especially with UVB. One can easily avoid this irritation by instructing the patient to apply calcipotriol after receiving ultraviolet light. Also, usually there appears to be no problem with patients applying calcipotriol more than two hours before receiving phototherapy. Therefore, most patients have no difficulties with applying calcipotriol in the morning and receiving phototherapy in the afternoon.

With regard to the combined use of calcipotriol with systemic agents, available data suggest the concurrent use of calcipotriol can significantly decrease the dosage requirements of oral medications used to treat widespread psoriasis. This enhancement resulting in a "dosage-sparing effect" of the systemic agent has been shown through scientific studies with cyclosporine, acitretin and methotrexate.[11–13]

Acitretin

Acitretin (Soriatane®), an oral retinoid which recently replaced etretinate (Tegison®), is one of three systemic agents approved for the treatment of psoriasis by the United States' FDA; methotrexate and cyclosporine are the other two. Acitretin performs poorly as a first-line agent in most patients with plaque-type psoriasis compared with the other two agents. It has a slower onset of action and often incompletely clears psoriatic lesions. At higher and presumably more effective doses, acitretin is poorly tolerated, having adverse effects such as hair loss, mucocutaneous side effects, myalgias, diarrhea.

On the other hand, this medication is an excellent first-line agent for elderly patients with psoriasis and patients with pustular psoriasis. And of the three systemic agents for psoriasis, acitretin is probably the safest one for long-term, maintenance therapy. Long-term use of methotrexate is associated with an increased risk of liver fibrosis and cirrhosis;[14,15] use of cyclosporine, an increased risk of nephrotoxicity and/or hypertension. There was an early concern that oral retinoids too might have their own detrimental effects, specifically on the skeletal system, with long-term use. A retrospective study had attributed diffuse idiopathic skeletal hyperostosis (DISH) syndrome to long-term etretinate therapy.[16] However, a more recent, prospective study on this syndrome in similar patients has generally failed to document any *de novo* appearance of bone spurs or any other skeletal changes.[17] This finding suggests that much of the bony abnormalities found in the earlier study were probably the result of degenerative bone disease rather than retinoid-induced changes. Besides possible skeletal effects, which seem less likely given more recent data, oral retinoids such as acitretin have not been associated with any other cumulative side effects, making acitretin an excellent choice for long-term, maintenance therapy. (For women of childbearing age, however, pregnancy must be avoided during and for three years after treatment, according to the FDA, due to potential teratogenic effects.)

In addition to maintenance monotherapy, acitretin has also been used effectively in combination with phototherapy. Even in doses as low as 25 mg/day, acitretin has been shown to greatly enhance both UVB and PUVA phototherapy.[18–21] These combinations are commonly referred to as "Re-UVB" and "Re-PUVA," respectively. Moreover, since there is a possible increased risk of skin cancer with phototherapy, acitretin may have an additional benefit in that it has been shown to decrease the risk of skin cancer.[22]

Treatment with acitretin also appears to be compatible with cyclosporine use, as first documented in transplant patients.[22,23] These patients were taking cyclosporine to prevent transplant rejection and acitretin to prevent warts and skin cancers. This combination appears to be safe, both in these studies and in the authors' experience, presenting no unusual side effects that one would not expect from one medication or the other if used independently. These medications are likely compatible given their metabolism by different hepatic isoenzymes and their different side-effect profiles, the exception being that both of these medications may increase serum cholesterol and triglyceride levels. Close monitoring of the lipid profile is therefore warranted when using this combination. The rationale behind using this combination in treating psoriasis will become readily apparent in the discussion on systemic sequential therapy below.

Cyclosporine

While dermatologists in the United States have had greater experience with calcipotriol compared to their colleagues in Japan, the opposite is true for cyclosporine. Cyclosporine was approved for dermatologic conditions many years ago in Japan; the FDA approved the medication for use in treating psoriasis in 1997. Partly due to unfamiliarity with this agent, dermatologists in the United States often reserve the use of cyclosporine for patients who are having particularly fulminant or extensive flares of psoriasis. At the maximum dermatologic dosage of 5 mg/kg/day, cyclosporine reliably acts rapidly, usually leading to complete or near-complete clearing of psoriatic plaques.[24]

Cyclosporine is a valuable addition to the systemic agents available in the United States, but the FDA has