

when applied faithfully twice per day, calcipotriol ointment was found to be overall significantly superior to fluocinonide ointment, a prototypical high-strength topical steroid used for treating psoriasis. An effective topical agent without the risk of skin atrophy, the odor, and the staining of steroids, tar, and anthralin, respectively, was finally available.

Early obstacles

While calcipotriol was embraced by many dermatologists and patients and became the most prescribed treatment for psoriasis since its introduction in the United States, some dermatologists met with disappointing results from using calcipotriol with their patients. The agent does have its inherent drawbacks. Approximately 20% of psoriatic patients are true non-responders to calcipotriol. Also, there is a 2% to 3% risk of developing persistent lesional irritation with this agent.

However, misuse of calcipotriol likely accounted for the majority of disenchanting experiences. First, because calcipotriol was only available as an ointment when introduced, some patients conceivably found the ointment greasy and inconvenient, applying it once per day instead of twice per day. Unbeknownst to both the patients and their dermatologists, using this agent once per day instead of twice per day essentially decreased the efficacy of calcipotriol by half.³ In addition, patients often expected results within two to three weeks, just as in the clinical trials, despite only once-per-day application. But they did not realize that the efficacy of once-per-day application approached that of twice-per-day application only after eight weeks of therapy.³ In other words, some patients and their dermatologists likely did not use calcipotriol for a sufficient period of time before judging it an ineffective treatment when using the agent as monotherapy once-per-day.

Another common mistake by some dermatologists was to abruptly discontinue a superpotent topical steroid and to try to replace it with calcipotriol as monotherapy. Well-intentioned dermatologists would start their patients on a superpotent steroid for more rapid clearing of psoriasis and then switch abruptly to the safer calcipotriol for long-term maintenance, instead of tapering the topical steroid. Unfortunately, some of these patients experienced steroid rebound: their psoriasis worsened due to the abrupt discontinuation of the steroid. Some dermatologists even went so far as to misinterpret steroid rebound as an allergic reaction to calcipotriol; when, in fact, a true allergy to calcipotriol is extremely rare. Once these mistakes were understood, better use of this agent emerged.

A better starting regimen: Calcipotriol with halobetasol

Eventually, clinical studies were conducted to try to optimize the use of calcipotriol. Lebwohl *et al.*⁴ conducted a multi-centered, double-blind trial which showed that the use of calcipotriol ointment once per day in the morning with the use of halobetasol propionate ointment (Ultravate[®]) once per day in the evening resulted in significantly faster responses among randomized psoriasis subjects than twice-per-day use of either ointment alone. In fact, as of this writing, this topical regimen is the most rapid and effective of any topical regimen for psoriasis documented in the scientific literature by a randomized, double-blind, multi-centered trial. The authors are not aware of any other regimen that works faster and better than a superpotent topical steroid ointment used twice per day.

Besides its superb efficacy, this combination of calcipotriol with halobetasol overcomes some drawbacks of calcipotriol mentioned above. For the few patients who truly do not respond to calcipotriol alone, the addition of halobetasol insures that these patients will receive at least one effective medication. Furthermore, it is the experience of the authors that some patients may not necessarily be true non-responders, but only relative non-responders: relative to the intensity of activity of the underlying psoriasis. That is, their psoriasis may be resistant to calcipotriol early on; but with some resolution after using a superpotent topical steroid, their psoriasis responds to calcipotriol. The combination of calcipotriol with halobetasol also was shown to minimize the risk of irritation from calcipotriol. In addition, this combination was found to be effective within two to three weeks, thus patients' patience need not be tested. The other drawbacks of calcipotriol will be addressed later in the discussion on topical sequential therapy.

Calcipotriol with phototherapy and with systemic agents

Other relevant information regarding calcipotriol use has been elucidated over the years. First, calcipotriol has been effective in enhancing psoralen-ultraviolet A (PUVA) phototherapy in every study conducted combining this agent with PUVA phototherapy.^{5,6} On the other hand, the results of clinical trials comparing the use of calcipotriol with ultraviolet B (UVB) phototherapy as compared to UVB phototherapy alone is mixed.⁷⁻⁹ Some of the studies showed some benefit, whereas others showed no additional benefit by adding calcipotriol to UVB phototherapy conducted three times per week. However, recently, Ramsay *et al.* reported that calcipotriol cream applied twice per day along with UVB phototherapy two times per week was as effective as UVB phototherapy conducted three times per week with the vehicle cream of calcipotriol