Vitamin D Receptor Polymorphism and Calcipotriol Response in Patients with Psoriasis

To the Editor:

Calcitriol, the physiologically active form of vitamin D, has been shown to induce an anti-proliferative response and differentiation in basal keratinocytes *in vitro*. These properties have led to the development of the noncalcaemic analog, calcipotriol, which has been used successfully in the treatment of psoriasis. Most of the pleiotropic actions of calcitriol are mediated by interaction with the vitamin D receptor (VDR), a member of the nuclear hormone receptor superfamily and a ligand-inducible transcription factor. Subsequent homodimerization or heterodimerization with a retinoic acid receptor-ligand complex precedes binding to the promoters of vitamin D-inducible genes. Several mutations in both the ligand and the DNA binding domains of the VDR gene have been demonstrated to be causative in patients with calcitriol-resistant rickets (Kristjansson *et al*, 1993).

Experiments examining the anti-proliferative effects of calcitriol demonstrated that ≈25% of psoriatic patients possessed dermal fibroblasts that exhibited partial resistance to calcitriol (Smith *et al*, 1988). In addition, recent studies involving assessment of VDR mRNA in psoriatic lesional biopsies taken from calcitriol and vehicle treated plaques reported that it was upregulated ≈2.4-fold in calcitriol-treated plaques, relative to vehicle treatment in responders. Conversely, no upregulation of VDR mRNA was observed in calcitriol-treated plaques from patients who displayed no significant improvement, suggesting that response to vitamin D therapy in psoriasis is determined by the ability to upregulate transcription or stability of this gene (Chen *et al*, 1996). We therefore hypothesized that alleles of polymorphic regions within the VDR gene may contribute to the observed phenomenon of nonresponsiveness to calcipotriol therapy in ≈25% of psoriatic patients. A single base transition in the human VDR gene characterized as a T for C change in intron 8, eliminating a *Bsm*I restriction site, has been strongly associated with low bone mineral density in certain populations (Morrison *et al*, 1994). Although it was initially suggested that this polymorphism may account for up to 75% of the total genetic effect on bone density, the association has been unreproducible in several other populations (Hustmyer *et al*, 1994; Looney *et al*, 1995).

We have analyzed this polymorphism in a local population of 92 patients with chronic plaque psoriasis using genomic polymerase chain reaction, restriction digestion, and agarose electrophoresis-based methodologies, and classified patients into calcipotriol responder groups, based on consistent evaluation of clinical parameters. The patients were managed and assessed by one dermatologist. They were prescribed calcipotriol ointment and asked to apply sufficient to produce a white layer over the plaques, up to a limit of 100 g per week, for a minimum of 4 mo. At 6-weekly follow-up visits, the compliance with therapy and response was assessed. The clinical response was graded on a linear analog scale, from 0 (no response) to 10 (complete clearance). Patients were then grouped into one of three clinical response categories, defined as minimal (0–3), intermediate (4–7), and excellent (8–10).

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Abbreviation: VDR, vitamin D receptor.

We found no correlation between VDR genotype and clinical responsiveness to calcipotriol in our population (**Table I**). No statistically significant differences were observed between any of the three groups and the frequency or carriage of either allele. In addition, we found no association between the polymorphism and psoriasis susceptibility in a larger psoriatic population of 175 individuals, either as a disease group overall or as subgroups, when divided into early and late-onset disease and compared with an ethnically matched, local control population of 124 individuals [allelic frequencies: b = 0.54, B = 0.46 (controls); b = 0.58, B = 0.42 (total psoriasis)]. Similarly, no correlation was observed between VDR alleles and severity of psoriasis, as assessed by division of patients into those undergoing systemic therapy and those using topical therapy alone.

These findings contrast with recently published data, reporting a strong association between responsiveness to topical and oral calcitriol therapy and the VDR *Bsm*I genotype in a psoriatic population of 48 individuals, in which 11 of 13 patients who exhibited a significant improvement following therapy carried the bb genotype, compared with none of 15 patients who demonstrated resistance to the treatment (Holick *et al*, 1996). These data indicate an association of the more common (b) allele with responsiveness to vitamin D treatment, and calcitriol therapeutic resistance has been reported to be associated with a failure to upregulate transcription of VDR mRNA following treatment; however, minigene reporter construct data suggested that the b allele is actually associated with lower transcription levels of the VDR gene (Morrison *et al*, 1994).

The discrepancy between the two studies may be explained by the differences in the sizes of population used, the use of calcitriol in the previous study, utilization of more sensitive genotyping methods in this study (polymerase chain reaction-based screening protocols, as opposed to Southern blot detection), and differences in the clinical assessment of response to vitamin D analogs. This study also confirms recent findings in a smaller Finnish population (Kontula *et al*, 1997) and excludes ethnicity of psoriatic populations as a possible factor influencing the present results. Further linkage studies utilizing proximal polymorphic markers and analysis of VDR mRNA sequences from psoriatic patients would be required to definitively exclude this gene as a candidate in the treatment of psoriatic lesions; however, the current data fail to support the hypothesis that alleles of the VDR gene contribute to either the resistance to calcipotriol therapy observed in ≈25% of patients, or the genetic susceptibility to psoriasis.

Table I. *Bsm*I polymorphism in the VDR gene does not correlate with response to calcipotriol treatment in 92 patients with chronic plaque psoriasis

		Genotype[a]			Frequency[b]		Carriage[c]	
Calcipotriol response	n	bb	bB	BB	b	B	b	B
Minimal	19	8	5	6	0.55	0.45	0.68	0.58
Intermediate	45	17	19	9	0.59	0.41	0.80	0.62
Excellent	28	11	11	6	0.59	0.41	0.79	0.61

[a]Number of individuals.
[b]Allelic frequencies within the responder groups.
[c]Carriage rates of each allele within responder groups.

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Localization of the Extracellular Domain of BPAG2 in Human Epidermal Basement Membrane

To the Editor:

The study by Masunaga *et al* in the August 1997 issue of the *Journal of Investigative Dermatology* used purified IgG developed against a baculovirus-encoded recombinant of BPAG2 to localize the ectodomain of this protein in human epidermal basement membrane. Re-evaluation of the BPAG2 cDNA used in this study found that it contained a single base substitution (C→T) resulting in a stop codon at nucleotide 4396 (GenBank accession number M91669). Hence, the baculovirus-encoded recombinant used to develop BPAG2-specific IgG lacked 68 amino acids at the carboxyl terminus of this protein. Consequently, our immunoelectron microscopy studies may have underestimated how far the carboxyl terminus of BPAG2 extends into the lamina densa of human epidermal basement membrane. BPAG2 remains the first molecule shown to extend from the cytoplasm of basal keratinocytes to the lamina densa of epidermal basement membrane.

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