

"Long-term durability and dose escalation patterns in infliximab therapy for psoriasis."¹ We appreciate their mentioning the 2011 study conducted by Kamili et al² and are pleased to learn that complementary results were reported in our study. Our article was intended to highlight the importance of higher dosing regimens with long-term infliximab therapy for psoriasis. Current evidence supports the observation that patients often require an infliximab dose that is higher than the standard 5 mg/kg every 8 weeks to maintain clearance. In all, 87% of the patients in the Kamili et al² study and 67% of the patients in our study required a higher infliximab dose.

In our experience, we have found that some insurers deny reimbursement for higher infliximab dosing schedules. Interestingly, Kamili et al² mention that 3 patients discontinued infliximab because of insurance problems. Although the exact nature of those insurance problems is not explained in the article, we also experienced many insurance barriers in providing necessary care to those patients who required larger doses of infliximab.

The use of infliximab for psoriasis may be restricted by cost, particularly when a higher dose is required. We hope that the conclusions reported by Kamili et al² and our study will assist providers' attempts to justify higher doses of infliximab to insurers. We greatly appreciate the input of Dr Mansouri and Dr Menter and encourage more studies and publications assessing long-term infliximab therapy for psoriasis.

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Filaggrin mutations as an archetype for understanding the pathophysiology of atopic dermatitis

To the Editor: Atopic dermatitis (AD) is a chronic disorder with strong associations connecting it with other atopic disease processes, such as allergic rhinitis, asthma, and food allergies. A complex interaction of genetic predisposition, environmental exposures, and immunologic mechanisms represent the still-nebulous milieu that drives the development of AD.^{1,2} In "Guidelines of Care for the Management of Atopic Dermatitis,"¹ Eichenfield et al discuss loss-of-function mutations in the filaggrin gene (*FLG*) as a risk factor strongly associated with the development of AD.¹ We contend that *FLG* provides a comprehensive framework for better understanding of AD and, in particular, the relationship of AD and sensitization to allergens.

FLG, encoded on chromosome 1q21, has long been associated with AD.^{2,3} The gene encodes profilaggrin, whose degradation leads to filaggrin, a protein critical in the terminal differentiation and maintenance of an effective skin barrier.^{1,4} Filaggrin is a prominent contributor to the stratum corneum's architecture and is further degraded to produce natural moisturizing factor.^{1,3} In addition to these roles in maintaining hydration and excluding foreign particles, filaggrin has also been reported to influence the skin's pH balance. *FLG* mutations deprive the skin of an important reservoir of acidic metabolites, resulting in an increase in protease function as well as impaired anti-staphylococcal activity, creating an inflammatory environment that may prime the immune response to foreign particles or allergens.² These varied effects draw the disparate arms of genetics, environment, and immunology together in a model centered on filaggrin.

Mutations in *FLG* have been identified in significant numbers of AD patients in European and Asian populations, with some estimates ranging as high as 56%.^{2,4,5} *FLG* mutations are rare in the African-American population, a significant limitation in advancing a broadly comprehensive model. However, a recent study by Margolis et al⁵ has identified mutations in the related filaggrin-2 (*FLG-2*) gene in the African-American population. *FLG-2*

produces a protein similar to filaggrin that appears to share many of the key functions discussed above. Furthermore, Margolis et al demonstrated a correlation with the development of persistent AD, as seen in *FLG* mutations.⁵

An additional facet of this model is the body of literature clearly linking *FLG* mutations with increased risk for development of other atopic processes and with sensitization to allergens.²⁻⁴ This creates an enhanced understanding of the “atopic march,” one in which a clearly defined genotype confers a strong predisposition toward developing an atopic phenotype. This connection rests on the impact that *FLG* gene defects impart: an impaired skin barrier, dysfunctional regulation of skin hydration and pH, and decreased antimicrobial ability, all of which foster a rich inflammatory environment prone to enhanced allergen exposure and immune sensitization.

FLG mutations cannot address the full spectrum of AD, but their manifold effects on the development and maintenance of an effective skin barrier gather the strands of genetics, environment, and immune mechanisms into a wide-reaching model. The recent identification of clinically relevant *FLG*-2 mutations and the growing body of evidence linking *FLG* mutations with allergic sensitization and atopic phenotype broaden and strengthen this model.

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Frontal fibrosing alopecia

To the Editor: We were interested to read the review of 355 cases of frontal fibrosing alopecia (FFA) in a Spanish population recently published in this journal by Vaño-Galván et al.¹ As the authors indicated, this intriguing condition is being seen with increasing frequency yet the cause(s) remain uncertain. In this cohort the majority (87%) were nonsmokers, however, this was not statistically different from age-matched unaffected Spanish women. In their commentary, the authors referred to a study we published in this journal in 2012,² suggesting we concluded smoking to be protective against FFA. This is a statement we must refute. Our aim in examining smoking status was to identify possible triggers for the condition. In agreement with the findings of Vaño-Galván et al,¹ we found that the majority of our patients were nonsmokers. Although the clinical significance of this observation was uncertain, we did not state nor intend to imply that smoking may be protective. Rather, the results from both studies would tend to exclude smoking as a possible trigger for the disorder. We consider this distinction essential to state categorically, to avoid dissemination of potentially harmful misinformation to patients with FFA.

There are several additional points on which we would be grateful for the authors' clarification. Firstly, with regard to disease pathogenesis, the authors propose FFA may be triggered by decreasing estrogen levels around the time of menopause. However, this hypothesis would not seem to explain the apparent increasing prevalence of the condition. Further, decreasing estrogen levels are perhaps a less attractive explanation for the increasing number of cases of FFA affecting premenopausal women and men.

Secondly, it would be valuable if the authors could comment further on their 3-point response to therapy scale, particularly in terms of cases of recorded improvement occurring in the context of a scarring alopecia. As the largest proportion of cases improving was seen in those treated with 5-alpha-reductase inhibitors, could this represent an improvement in female pattern hair loss, found in 40% of their cases? A proportion of cases were also receiving treatment with topical minoxidil. In addition, with