ONLINE FIRST

Effect of Nutrient Supplementation on Atopic Dermatitis in Children

A Systematic Review of Probiotics, Prebiotics, Formula, and Fatty Acids

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Objective: To identify whether nutrient supplementation with probiotics, prebiotics, formula, or fatty acids prevents the development of atopic dermatitis (AD) or reduces the severity of AD in newborns to children younger than 3 years.

Data Sources: We searched MEDLINE, Cochrane Central Register of Controlled Trials, and LILACS (Latin American and Caribbean Health Science Literature) from January 1, 1946, to August 27, 2012, and performed an additional manual search.

Study Selection: Randomized controlled trials and cohort studies examining nutritional supplementation in prevention and amelioration of AD among children younger than 3 years.

Data Extraction: Of 92 articles, 21 met inclusion criteria.

Data Synthesis: In the 21 studies, a total of 6859 participants received supplements, which included infants or mothers who were either pregnant or breastfeeding; 4134 infants or mothers served as controls. Nutritional supplementation was shown to be an effective method in preventing AD (11 of 17 studies) or decreasing its severity (5 of 6 studies). The best evidence lies with probiotics supplementation in mothers and infants in preventing development and reducing severity of AD. Specifically, *Lactobacillus rhamnosus* GG was effective in long-term prevention of AD development. γ-Linolenic acid reduced severity of AD. Supplementation with prebiotics and black currant seed oil (γ-linolenic acid and ω-3 combination) was effective in reducing the development of AD. Conflicting findings were reported from different research groups that performed supplementation with an amino acid–based formula.

Conclusions: Certain types of nutrient supplementation are beneficial in preventing AD development and reducing its severity. Future research elucidating the mechanisms underlying the actions of nutritional supplementation on AD is necessary.

Arch Dermatol.
Published online December 17, 2012.
doi:10.1001/jamadermatol.2013.1495

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ATOPIC DERMATITIS (AD) IS the most common chronic inflammatory skin disease in infants.[1] The incidence of infant AD has increased during the last 30 years, with 20% of infants and young children experiencing symptoms.[2] Infant AD is associated with respiratory diseases such as asthma and hay fever, which manifest in early adulthood.[2] Nutrient supplementation is potentially helpful in the prevention of AD and in the reduction of its severity. Many researchers have suggested that supplementation with specific nutrients, such as probiotics, partially hydrolyzed whey protein formula, or other formulas, may prevent the development of AD or decrease its severity.[2,3] Although some studies have found specific nutrient supplementation effective, conclusions vary among study outcomes. The objective of this systematic review was to assess how the addition of nutrient supplements affects the development and severity of AD in children younger than 3 years.

METHODS

DATA SEARCH

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and LILACS (Latin American and Caribbean Health Science Literature) database for articles published from January 1, 1946, to August 27,

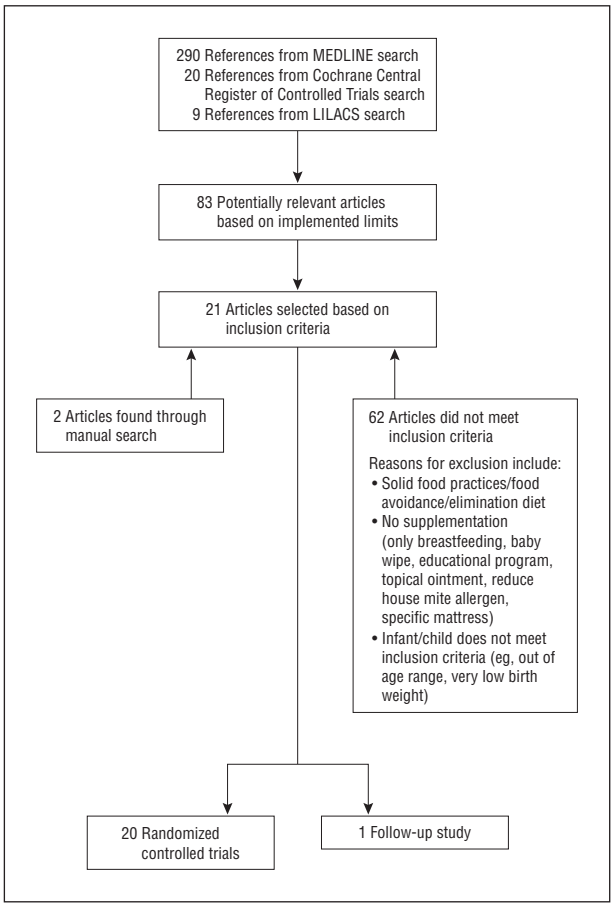

Figure 1. Flowchart of selected studies for systematic review.

2012. For MEDLINE, the following Medical Subject Heading (MeSH) terms were combined using the AND command:

- Dermatitis, Atopic/diet therapy [MeSH] OR Dermatitis, Atopic/prevention and control [MeSH]
- Infant [MeSH]

The following terms were combined using the AND command to find relevant studies on the Cochrane Central Register of Controlled Trials and LILACS database:

- Atopic dermatitis
- Infants
- Nutrition

An additional search was conducted on LILACS using the AND command:

- Atopic dermatitis
- Nutrition
- Infant
- Prevention

Search results were limited to articles that studied infants aged 0 to 23 months or children aged 2 to 3 years. A manual search through references of the chosen articles supplemented our search strategy.

INCLUSION AND EXCLUSION CRITERIA

After reading individual abstracts, we included clinical trials and cohort studies that examined the effect of nutrient supplements on AD in children younger than 3 years.[4] Studies that reported prevalence, incidence, or AD severity were selected. Furthermore, studies were chosen that included children who were either at risk for developing AD or have AD. Researchers used specific criteria to diagnose AD and the Scoring Atopic Dermatitis (SCORAD) index to assess the severity of AD among study subjects.[5-8] Publications were excluded if the intervention included preterm infants, if mothers or infants were not given a nutrient supplement, or if the effect of supplementation on the development or severity of AD was not a primary outcome.

STUDY SELECTION AND DATA EXTRACTION

On the basis of selection criteria, 2 authors (N.F. and E.A.B.) reviewed all 21 articles independently and resolved any differences by consensus. Two authors (E.P.C. and A.W.A.) reviewed some of the studies. From each study, information was abstracted regarding the type of nutrient, duration of supplementation and follow-up, and primary and secondary outcome measures. Specifically, subject characteristics for mothers and infants, family history, and primary and secondary measures of association were collected (eTable 1 and eTable 2; http://www.archdermatol.com). We assessed the risk of bias for all studies by examining selection bias, performance bias, measurement bias, and attrition bias (eTable 3).

RESULTS

The MEDLINE search resulted in 290 articles initially; after application of the aforementioned limits, 63 articles remained. Among these, 19 articles were selected for meeting inclusion and exclusion criteria. The Cochrane Central Register of Controlled Trials search initially yielded 20 articles; after reviewing the abstracts, 2 articles were selected. The LILACS searches resulted in 9 articles; after reviewing the abstracts, none were selected. A manual search resulted in 2 additional relevant articles, for a total of 21 full-text articles that met the inclusion criteria (20 randomized controlled trials [RCTs] and 1 study documenting follow-up data to an RCT) (**Figure 1**). In the 21 studies, a total of 6859 participants received supplements, which included infants or mothers who were either pregnant or breastfeeding; 4134 infants or mothers served as controls. Thirteen studies focused on infants with a family history of atopic disease[9-21]; 6 studies recruited infants who did and did not have a family history,[22-27] and 1 study focused on infants without a family history of atopic disease.[28] The majority of probiotic studies supplemented both mothers and infants.[9-11,13,18,22]

PROBIOTICS

Probiotics are foods that are composed of the same live bacteria that are present in the gut microflora.[29] Ten studies (9 RCTs and 1 follow-up study documenting data to a RCT) provided probiotics to either children alone or to both the children and their mothers during the prenatal and postnatal periods (eTable 1 and eTable 2).* Spe-

**References 9-11, 13, 14, 18, 22, 23, 27, 30.*

cifically, 7 of the 10 studies examined single probiotics, and 3 studies examined mixtures of probiotics.

Single Probiotics

Studies that examined single probiotics evaluated *Lactobacillus rhamnosus* GG, *L rhamnosus* strain HN001, *Bifidobacterium animalis* subsp *lactis* strain HN019, and *Lactobacillus acidophilus* LAVRI-A1. The preponderance of evidence appears to suggest that *L rhamnosus* GG may be beneficial in preventing the development of AD. Specifically, when *L rhamnosus* GG was given to both pregnant mothers and infants at risk for developing AD, the frequency of AD in infants from the group supplemented with the probiotic was half of that of the placebo group (relative risk [RR], 0.51 [95% CI, 0.32-0.84]).[9] The authors concluded that *L rhamnosus* GG could prevent AD among at-risk infants. In the follow-up study of these infants, the addition of the probiotic *L rhamnosus* GG in mothers and infants during the prenatal and postnatal periods prevented the development of AD 2 years beyond infancy (RR, 0.57 [95% CI, 0.33-0.97]) (eTable 2).[10] During the follow-up period, researchers invited subjects to complete a questionnaire to ascertain information about supplementation. Of note, when these children who received *L rhamnosus* GG during the prenatal and postnatal periods were followed until 7 years of age, they continued to have significantly reduced incidence of eczema compared with the placebo group (RR, 0.64 [95% CI, 0.45-0.92]).[31] However, 1 study did not find a protective effect of *L rhamnosus* GG in preventing the development of AD (RR, 0.96 [95% CI, 0.38-2.33]).[13]

Other single probiotic supplementations included *L rhamnosus* strain HN001, *B animalis* subsp *lactis* strain HN019, and *L acidophilus* LAVRI-A1 (eTable 1 and eTable 2). Supplementation with *L rhamnosus* strain HN001 in prenatal and postnatal mothers and infants significantly reduced the risk of developing eczema in high-risk infants during the first 2 years of life (hazard ratio, 0.51 [95% CI, 0.30-0.85]).[18] Of note, *B animalis* subsp *lactis* strain HN019 given to prenatal and postnatal mothers and infants did not appear to prevent AD development in high-risk infants during the first 2 years of life.[18] Supplementation of *L acidophilus* LAVRI-A1 in infants whose mothers had allergic disease did not prevent AD development.[14]

Probiotic Mixes

Rather than single probiotic supplementation, probiotic mixes have become more widely used in preventing AD development during the last decade. In a study involving 112 pregnant mothers who later gave birth to infants enrolled in the study, infants receiving the probiotic mix (*Bifidobacterium bifidum* BGN4, *Bifidobacterium lactis* AD011, and *L acidophilus* AD031) had significantly reduced prevalence and incidence of AD (odds ratio [OR], 0.26 [95% CI, 0.07-0.98], and OR, 0.24 [95% CI, 0.075-0.792], respectively). Therefore, this probiotic mix appeared to be effective in preventing eczema in the first year of life for at-risk infants.[11]

A different probiotic mix composed of *L rhamnosus* GG, *L acidophilus* La-5, and *B animalis* subsp *lactis* Bb-12 was given to mothers during the prenatal and postnatal periods. This probiotic mix significantly reduced the cumulative incidence of AD among infants in the probiotic group (OR, 0.51 [95% CI, 0.30-0.87]).[22] Furthermore, when stratifying the infants based on whether they had a family history of atopic disease, a significantly reduced odds of AD was revealed among those without a family history (OR, 0.09 [95% CI, 0.01-0.77]). In another study examining a different probiotic mixture, researchers supplemented preschool children who were previously diagnosed as having AD with a probiotic mix composed of *L acidophilus* DDS-1 and *B lactis* UABLA-12 with fructooligosaccharide.[23] Researchers found a significant reduction in AD severity after supplementation ($P=.001$) (eTable 1 and eTable 2).[23]

Probiotics and Formula

In 2 studies, researchers supplemented extensively hydrolyzed whey formula with probiotics.[27,30] Researchers supplemented extensively hydrolyzed whey formula with either *L rhamnosus* GG or *B lactis* Bb-12. During and after supplementation, a significant decrease in AD severity was reported among infants in the intervention group ($P=.01$ and $P=.002$).[27] In a separate study, researchers supplemented formula with viable or heat-inactivated *L rhamnosus* GG.[30] After supplementation, researchers reported a significant reduction in AD severity among all infants.

PREBIOTICS

Prebiotics are specific nondigestible oligosaccharides that stimulate the growth of certain types of bacteria in the colon.[29] Prebiotics differ from probiotics in that prebiotics assist the survival of the microflora of the colon, whereas probiotics contribute to the intestinal flora. In one study, researchers supplemented low-risk infants with a prebiotic formula composed of neutral short-chain oligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) at a ratio of 9:1 (85%) and specific pectin-derived acidic oligosaccharides (15%).[28] Infants supplemented with the prebiotic formula had a significantly lower risk of developing AD than those in the placebo group (hazard ratio, 0.56 [95% CI, 0.323-0.971]). Alternatively, the severity of AD between the 2 groups was not significantly different ($P=.08$ and $P=.71$) (eTable 1 and eTable 2). In one study, researchers supplemented infants with a prebiotic formula composed of scGOS and lcFOS (8 g/L of scGOS-lcFOS).[19] Researchers reported a reduction in AD incidence by greater than 50% ($P<.05$). Researchers concluded that the specific prebiotic formula is an effective method of preventing AD among low-risk infants.[28]

FORMULA

In some instances when breastfeeding is not sufficient, a partially hydrolyzed formula or extensively hydrolyzed formula may be recommended for infants who are

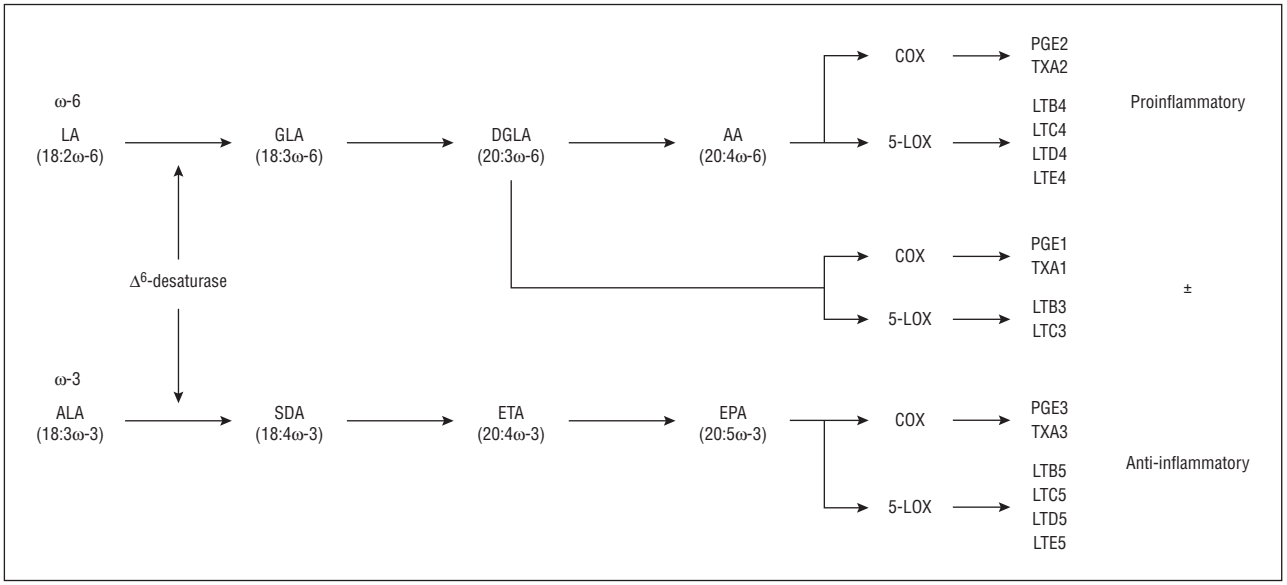

Figure 2. Metabolism of ω-3 and ω-6 fatty acids and the associated inflammatory responses. 5-LOX indicates 5-lipooxygenase pathway; AA, arachidonic acid; ALA, α-linolenic acid; COX, cyclo-oxygenase pathway; DGLA, dihomo-γ-linolenic acid; EPA, eicosapentaenoic acid; ETA eicosapentaenoic acid; GLA, γ-linolenic acid; LA, linoleic acid; LTB, leukotriene B; LTC, leukotriene C; LTD, leukotriene D; PGE, prostaglandin E; SDA, stearidonic acid; TXA, thromboxane. The ± sign indicates the range of proinflammatory to anti-inflammatory response. Modified from Linnamaa et al,[25] with permission.

at risk for allergic diseases.[17] Hydrolyzed or partially hydrolyzed formulas involve the breakdown of whey protein into smaller pieces for easier digestion. Alternatively, infants with cow's milk allergy or intolerance will be given an amino acid–based formula.[24] Five studies supplemented at-risk infants with either hydrolyzed formula or an amino acid formula.[16,17,21,24,26] Researchers supplemented infants with 1 of 4 possible formulas: cow's milk formula, partially hydrolyzed whey formula, extensively hydrolyzed whey formula, or extensively hydrolyzed casein formula.[17] Researchers reported that infants receiving the extensively hydrolyzed casein formula had a significantly lower odds of allergic manifestations compared with those receiving cow's milk formula (OR, 0.53 [95% CI, 0.29-0.98]). Groups given partially hydrolyzed whey formula and extensively hydrolyzed whey formula had a statistically nonsignificant reduction in the incidence of allergic manifestations compared with those receiving cow's milk formula (OR, 0.65 [95% CI, 0.39-1.10], and OR, 0.90 [95% CI, 0.55-1.55], respectively).[17] In the follow-up study of these infants, researchers found a significantly reduced cumulative incidence of AD among infants supplemented with partially hydrolyzed whey formula (OR, 0.60 [95% CI, 0.37-0.97]) and extensively hydrolyzed casein formula (OR, 0.53 [95% CI, 0.32-0.88]) from birth to the third year of life. This finding indicated that the development of atopic disease was not postponed.[16] In one study, researchers supplemented infants with a protein hydrolysate formula and measured AD incidence and severity.[21] The infants who were supplemented with formula had significantly fewer cases of AD ($P < .01$ at 2 years and $P < .01$ at 4 years). No significant differences were reported in the severity of AD between the 2 groups.[21] Investigators from 2 studies supplemented infants with an amino acid–based formula, and researchers measured the severity of AD. One study revealed a significant improvement in SCORAD mean score (SCORAD mean score, 10.7 [95% CI, 7.1-14.2]) (eTable 1 and eTable 2)[26]; however, the other study did not find similar results.[24]

FATTY ACIDS

γ-Linolenic acid (GLA), 1 type of ω-6 fatty acid, is the precursor for prostaglandin E_1 as well as other inflammatory mediators. γ-Linolenic acid has some noninflammatory properties compared with the proinflammatory effects of other ω-6 fatty acids (**Figure 2**).[32] Researchers hypothesize that prostaglandins assist in the development and maturation of the immune system.[33] A decrease in the conversion of linoleic acid leads to decreased GLA levels, which may be associated with AD development later in life (Figure 2).[12,15] In 2 studies, researchers supplemented infants alone or both mothers and their infants with GLA to measure whether it affects the development and severity of AD among at-risk infants.[12,15] After supplementing infants of mothers with atopic disease, researchers reported a favorable trend in the reduction of AD severity among infants ($P = .06$). No significant differences in incidence of AD and serum IgE were found between the GLA and placebo groups. Researchers concluded that GLA was associated with a reduction of the AD severity (OR, 0.67 [95% CI, 0.32-1.39]). However, studies found that GLA supplementation did not prevent AD development.[12,15]

Some studies suggest that black currant seed oil (BCSO), which is rich in ω-3 and ω-6 fatty acids, could be beneficial in the development of the atopic immune response.[25] The ω-6 fatty acid in BCSO is GLA. Black currant seed oil is 13% GLA and 14% α-linolenic acid.[25] In one study, researchers supplemented mothers and infants with BCSO and found a significantly reduced prevalence of AD only among the supplemented 12-month-

old infants ($P=.04$). The authors concluded that BCSO may prevent AD symptoms when given as a supplement at an early age.[25]

In one study, researchers followed up infants whose mothers had previously been supplemented with ω-3 long-chain polyunsaturated fatty acid during the second half of their pregnancy.[20] At 1 year of age, although there was no reduction in the incidence of IgE-associated allergies, AD with sensitization was lower among infants whose mothers had been supplemented with long-chain polyunsaturated fatty acid (RR, 0.64 [95% CI, 0.40-1.03]).[20]

QUALITY ASSESSMENT AND RISK OF BIAS

Study qualities were tabulated from the 21 studies (eTable 3). The majority of studies (14 of 21 articles) maintained a completion rate greater than 70%.† The remaining studies demonstrated moderate completion rates ranging between 40% and 70%.[11,16,17,20,25] The majority of studies recruited subjects with similar medical histories and demographics and subsequently randomized and blinded them to the treatment. Likewise, the health care providers were blinded, and allocation was concealed. As a result, the risk of bias is low among the selected studies (eTable 3).

COMMENT

On the basis of this systematic review, certain nutrient supplements may prevent the development of AD or diminish its severity among infants and children younger than 3 years. Of the 21 selected studies, a majority found that certain nutrition supplementation was able to prevent the development (11 of 17 studies)[9-11,16-18,20-22,25,28] or severity (5 of 6 studies)[15,23,24,26,27] of AD. Specifically, supplementation with probiotics was the most commonly studied nutrient, where a majority of studies found that supplementation with certain probiotics reduced the incidence of AD.[9-11,18,22,31] Certain probiotics have a positive impact in utero and in infants, when supplementation could lead to decreased AD development. Prebiotics stimulate the growth of the microflora of the colon. Researchers reported a reduced risk of developing AD with the use of prebiotic supplementation; however, a significant difference was not found in reducing the severity of AD.

Supplementation with formula is a necessity at times when breastfeeding is not possible. The formulas that were used resulted in different degrees of AD prevention because of the various processing methods present.[16] Hydrolyzed or partially hydrolyzed formulas are composed of smaller pieces of whey protein for easier digestion. Partially hydrolyzed whey formula and extensively hydrolyzed casein formula were found to be an effective method in preventing the development of AD, especially among infants without a family history.[16,17] Specifically, among children with a family history of AD, extensively hydrolyzed casein formula had a greater positive effect on preventing AD development. This review showed that ω-3 and ω-6 fatty acids such as GLA reduced AD severity among infants but did not prevent AD development. Further research is required to measure the effects of GLA supplementation on prevention of AD. Black currant seed oil, a combination of ω-3 and GLA, was found to be beneficial in preventing AD development.[25] Of note, sources of GLA include borage oil,[15] which may contain traces of pyrrolizidine alkaloids. Current research suggests possible toxic effects from pyrrolizidine alkaloids; however, the effects of these trace substances on human physiology are not yet well understood.[34,35]

Differences in study methodology can culminate in divergent results and conclusions in studies evaluating the same nutritional supplement. Specifically, length of supplementation, length of follow-up period, and selection of nutrient varied among the selected studies and may have resulted in the inconsistent outcomes. Many researchers have turned to nutrient supplementation as a potential tool for prevention and reduction in severity of AD. When an expectant mother has a family history of AD or when an infant is diagnosed as having AD, parents frequently inquire whether they should augment their diet or their child's diet. Based on the available studies, the best evidence supports supplementing infants alone or both mothers and their infants with certain single probiotics (eg, *L rhamnosus* GG) or with a mix (*L acidophilus* DDS-1 and *B lactis* UABLA-12). For infants or children with AD, supplementation with GLA may have a positive effect on reducing AD severity.

Our systematic review revealed that nutritional supplementation may be an effective method in both preventing AD[9-11,16-18,20-22,25,28] and decreasing its severity[15,23,24,26,27] among infants. From the currently available literature, more studies are required before we draw conclusions about the effectiveness of BCSO, prebiotics, and formula. Future studies can explore the mechanisms underlying the prevention of AD with nutrient supplementation. Furthermore, the literature lacks longitudinal research, including follow-up studies, which can evaluate whether nutrient supplementation in infancy results in lasting preventive effects. Future studies evaluating combinations of supplements such as probiotics and GLA may result in synergistic effects on prevention and reduction in severity of AD. As researchers continue studying the effects of nutrient supplements on the prevention and severity of AD, their findings will contribute to new therapeutic options to benefit infants and children with AD.

Accepted for Publication: September 20, 2012.
Published Online: December 17, 2012. doi:10.1001/jamadermatol.2013.1495
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Author Contributions: Ms Foolad and Dr Armstrong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Foolad, Chase, and Armstrong. *Acquisition of data:* Foolad and Brezinski. *Analysis and interpretation of data:* Foolad, Brezinski, Chase, and Armstrong. *Drafting of the manuscript:* Foolad. *Critical revision of the manuscript for important intellectual content:* Foolad, Brezinski, Chase, and Armstrong. *Statistical analysis:* Foolad, Brezinski, Chase, and Armstrong. *Administrative, technical, and material support:* Armstrong. *Study supervision:* Armstrong.

Conflict of Interest Disclosures: Dr Armstrong is an investigator and consultant to Modernizing Medicine, Abbott, Amgen, and Janssen.

Online-Only Material: The 3 eTables are available at http://www.archdermatol.com.

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