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Recent Considerations in the Use of Recombinant Interferon Gamma for Biological Therapy of Atopic Dermatitis

Kanwaljit Brar, MD and **Donald Y. M. Leung, MD, PhD**

Division of Pediatric Allergy-Immunology, Department of Pediatrics, National Jewish Health, 1400 Jackson Street, Denver, CO 80206

Abstract

Introduction—Atopic dermatitis (AD) is the most common inflammatory skin disease in the general population. There are different endophenotypes of AD that likely have a unique immune and molecular basis, such as those who are predisposed to eczema herpeticum, or S*taphylococcus aureus* infections.

Areas Covered—In this review, we highlight the endophenotypes of AD where reduced interferon gamma expression may be playing a role. Additionally, we review the potential role of recombinant interferon gamma therapy in the treatment of atopic dermatitis and the particular phenotypes that may benefit from this treatment.

Expert Opinion—Recombinant interferon gamma treatment will likely benefit the pediatric population with AD, as well as those with susceptibilities for skin infections. Future studies are needed to elucidate whether IFN-γ may reduce the prevalence of skin infection in AD.

Keywords

atopic dermatitis; biological; interferon gamma; eczema herpeticum; skin infection

1. Introduction and Background

1.1. Introduction

Atopic dermatitis (AD) is a complex, inflammatory skin disease with multiple genetic and immune pathways that may respond to different therapeutic approaches. Leung et al previously described multiple clinical phenotypes of AD based upon age of onset, severity, race, presence of IgE sensitization and predisposition towards infection [1,2]. One such phenotype are those individuals with AD that have increased colonization with *Staphylococcus aureus*, and another phenotype is those that have predisposition towards eczema herpeticum. Individuals with AD with predisposition for skin infections are more likely to have mutations affecting the filaggrin protein [3–4]. Filaggrin functions to decrease

Address correspondence to: Donald YM Leung, MD, PhD, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, Tel: 303-398-1379, Fax: 303-270-2182; leungd@njhealth.org.

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the skin pH thereby improving the skin's ability to fight these microorganisms [5]. Filaggrin-dependent secretion of sphingomyelinase also protects against staphylococcal α-toxin-induced keratinocyte death [6]. AD patients with predisposition towards cutaneous infections have alterations in their skin pH, microbiome, and innate and adaptive immune systems including expression of antimicrobial peptides as well as T-cell balance [1]. Biomarkers are being identified that may help differentiate clinical subsets of AD into unique endotypes using genetic and immune profiling approaches. This differentiation would allow for a precision medicine approach to their treatment regimen and account for individual co-morbidities, such as predisposition towards food allergy or infectious complications.

At present, the mainstay of AD treatment is topical corticosteroids, or topical calcineurin inhibitors, with use of systemic immunosuppressants, such as cyclosporine, or mycophenylate mofetil for more severe cases. The clinical management of AD will likely shift towards increased use of biologics, targeting the major pathways in the immunopathogenesis of AD. One such example is the treatment of moderate-to-severe AD in adults with Dupilumab, a fully human mAB targeting the IL-4Rα, which is required for both IL-4 and IL-13 action [7]. In phase I trials of Dupilumab in adults, a dose-dependent clinical improvement was seen, as well as an improvement in the molecular signature of skin biopsies from AD lesions [7]. There were decreases in gene expression related to epidermal hyperplasia, immune cells, and chemokines of the Th2 pathway [8]. Although Dupilumab targets the Th2 pathway, it seems to have efficacy regardless of the patient's serum IgE level [8]. It should be noted, however, that IgE to specific allergen can be elevated even with normal total serum IgE levels.

Recombinant interferon gamma (rIFN-γ) is an immunomodulatory agent previously studied in the treatment of moderate-to-severe AD. IFN-γ is a type II interferon involved in Th1 cell differentiation and is distinguished from other interferons by its immunomodulatory activity [9]. It is produced by T lymphocytes and by Natural Killer cells stimulated by microbes. It acts via the transcription factors T-bet, the master regulator of Th1 differentiation, as well as STAT1 and STAT4. IFN-γ is also known to inhibit Th2 differentiation. Recombinant interferon gamma (rIFN-γ) is a subcutaneous (SQ) treatment that is the standard of care in chronic granulomatous disease (CGD) [10–11]. It may also benefit patients with severe AD, particularly AD patients colonized with *S. aureus*, and with predisposition towards eczema herpeticum (ADEH+) as we postulate it would enhance their ability to "fight" these infections as in CGD [12–13]. In this review, we will discuss the rationale for use of rIFN-γ in the treatment of selected subsets of AD patients who are deficient in IFN-γ production.

2. Role of IFN-γ in AD

In AD, many factors contribute to the alteration of the Th1/Th2 balance to favor the atopic Th2 pathway, leading to IgE mediated sensitization. Thymic stromal lymphopoeitin (TSLP) is an IL-7 like cytokine that is expressed by keratinocytes in AD, and can activate dendritic cells in the skin to direct T cells towards production of Th2 cytokines, thereby facilitating the atopic march [14]. In one study, risk factors for development of atopy, which included development of AD, was having two atopic parents, parental smoking, and AD in one parent

[15]. Infants have impaired IFN-γ activation and increased IL-4 cytokine production leading to this predisposition [15–16]. Cord blood samples of children who go on to develop atopy or AD have impaired allergen-induced IFN-γ production, and reduced IFN-γ levels in cord blood may be a better predictor of AD than cord blood IgE levels [15–17]. Other reasons for the Th1/Th2 imbalance is that IFN-γ producing Th1 cells undergo increased apoptosis or activation-induced cell death (AICD) via the Fas/FasL pathway [18]. Thus, IFN-γ may alter the T helper cell profile in the atopic patient [18].

Patients who present with AD in infancy may vary in their genetic or immune characteristics from those presenting in adolescence or adulthood. A recent study by Czarnowicki et al reported that there is a severe deficiency of T cell derived IFN-γ in children with AD. Interestingly this was restricted to skin-homing T cells that are positive for cutaneous lymphocyte antigen (CLA+) [19]. In their study, 19 children less than 5 years with AD were found to have significantly greater reduction in expression of IFN-γ/CLA+ levels in peripheral blood than healthy control children. The pediatric AD population also had lower CLA + and CLA − Th1 cell population in peripheral blood when compared with adults with AD [19]. In contrast, the adult T cell population was found to have increased expression of Th22 cells, as well as HLA-DR, particularly in the CLA+ cells compared with controls, but not IFN-γ [19]. These data suggest that adults may not benefit as much from IFN-γ therapy, as children. This may be particularly true, as other studies have demonstrated reduced IFN-γ in children with AD as early as the newborn period as measured through cord blood samples [15–16].

2.1. Effect of IFN-γ on Keratinocytes

IFN-γ has multiple effects on epidermal keratinocytes. It has been shown to up-regulate HLA-DR in keratinocytes, and a specific HLA-DRB1 polymorphism has been associated with AD in Korean children [20]. IFN-γ also acts on keratinocytes to affect leukocyte migration in the epidermis via effects on particular chemokines in AD [21]. In a study by Giustizieri, et al [21], cultured keratinocytes from patients with AD, psoriasis, and healthy controls were stimulated with cytokines. When the keratinocytes were stimulated with IFN-γ, there was an up-regulation of monocyte chemoattractant protein1 (MCP-1) and IFN-γ–induced protein of 10 kd (IP-10)/CXCL10 [21]. This is consistent with the concept that IFN-γ plays a more pathologic role in psoriasis whereas a lack of IFN-γ enhances atopy.

2.2. Role of IFN-γ in cutaneous infections complicating AD

IFN-γ, and its receptor have been shown to play an important role in the pathogenesis of ADEH+. ADEH+ is viewed as a distinct phenotype of AD, since less than 5% of patients with AD are prone to disseminated skin infection with herpes simplex virus (HSV) infection. Susceptibility to HSV in AD is likely due to multiple factors including deficient innate as well as adaptive immune responses to HSV, and defects in the skin barrier [1,12]. Patients with AD also have increased susceptibility to other cutaneous viral infections, such as vaccinia virus, coxsackie virus, and molluscum contagiousum [22–24]. Atypical hand-foot-mouth disease, caused by the coxsackie strain CV-A6 has been known to complicate the rash in patients with underlying AD. This rash termed “eczema coxsackium” has been described in children and adults [25–26]. It is not known if IFN-γ is involved in

predisposition towards CV-A6 in individuals with AD, and its potential role needs to be investigated further.

Previous studies have shown an odds ratio of greater than 10 for filaggrin (FLG) null mutations in ADEH+ subjects, and an increased association of ADEH+ with gene variants in thymic stromal lymphopoietin (TSLP), which results in APC-directed Th2 differentiation [3, 27]. There have also been genetic variants identified in the interferon superfamily, as well as their regulators in ADEH+ individuals. Gene variants include IFN-alpha receptor 1 (IFNAR1), IFN-gamma receptor 1(IFNGR1), interferon regulatory factor 2, 3, 7 (IRF2, IRF3, IRF7), as well as IFNG, and IFNGR [12, 28–29]. IFNGR1 may play a role in controlling viral infections, including HSV, as rare individuals with primary immunodeficiency resulting in IFNGR loss of function had more severe HSV infections, such as encephalitis [30].

Genetic variation in the IFNG gene in ADEH+ patients has been demonstrated in a study by Leung et al [12]. Using GeneChip profiling of PBMCs from individuals who were ADEH+, the investigators found that those patients with susceptibility towards HSV infection had statistically significant lower gene expression of IFNG and IFNGR compared with those AD who did not have a history of eczema herpeticum (ADEH−) and non-atopic controls. In addition to differences in gene expression, IFN-γ protein levels measured by ELISA or spot forming cells were also lowest in the ADEH+ group after stimulation with HSV. IFN-γ protein expression may be useful as a biomarker to identify the AD subtype associated with increased susceptibility to disseminated viral skin infections [12]. In this study, they also identified single nucleotide polymorphisms (SNPs) in the IFNGR1 and IFNG that increased risk for ADEH+, and found differences in mortality of a knockout mouse model of the IFNGR gene compared with the wild type control [12]. There are additional rare variants in the interferon pathway that were identified in a recent study by Gao et al, where targeted deep sequencing was performed on a European-American and African-American cohort with susceptibility to eczema herpeticum [31]. Through DNA sequencing, they also identified functional haplotypes in the IFNGR1 gene associated with susceptibility to the ADEH+ phenotype [31].

Another study looking at RNA transcriptional changes in ADEH+ by Bin et al, found significant down-regulation of 15 genes within the interferon superfamily, including Type I and type III Interferons [29]. They also found inhibition and reduced gene expression of IRF3 and IRF7 in HSV-stimulated PBMCs from the ADEH+ subjects. This indicates that those with the ADEH+ phenotype have attenuation of their interferon pathway resulting in an immune system that is more susceptible to cutaneous infection.

Reduced IFN-γ production may also be involved in the pathway of patients with AD complicated by *S. aureus* colonization. A study by Machura et al looking at children with AD found that 97.5% of these children were colonized with *S. aureus*, compared with 0% of the control group [13]. In this colonized group, they found reduced IFN-γ release from CD4+ and CD8+ cells stimulated by PMA and ionomycin [13].

3. Clinical data on recombinant IFN-γ (rIFN-γ) treatment of AD

There are multiple clinical trials investigating the efficacy of rIFN-γ in AD patients. IFN-γ in a subcutaneous form has been used as a treatment for severe AD [32]. The first clinical trial looking at rIFN-γ for the treatment of AD was done by Boguniewicz et al, in 1990, in 22 patients with chronic severe AD [32]. Patients were treated with escalating doses of rIFN-γ in Part I of the study with 0.01 mg/m^2, 0.05 mg/m^2, and 0.1 mg/m^2, and in Part II they were treated with 0.05 mg/m^2 by daily SQ injection for 6 weeks, and then three times weekly during the maintenance phase. The median age of the subjects in parts I and II were 33 years and 25 years respectively though pediatric subjects were also enrolled. In both parts of this study, patients were found to have improvement in clinical severity, which was sustained during the maintenance phase in part II of the study. In Part I of the study, there was a worsening of skin severity 3 days after discontinuation of therapy. Serum IgE were not observed to change in both parts [32].

Another study looking at rIFN-γ treatment for AD was a combined pediatric and adult study by Hanifin et al [33]. This was the first double-blind placebo-controlled trial of rIFN-γ for the treatment of severe AD [33]. In this study, 83 patients with moderate to severe AD were randomized to be treated with rIFN-γ dosed at 50 μg/m^2 daily SQ for 12 weeks or a placebo [33]. Forty patients were randomized to treatment, while 43 were randomized to placebo. The median age was 37 years and 28 years respectively in the two groups, and only 6 children participated. Though the pediatric cohort was smaller, their study found a better response in the pediatric population, when compared with adults, with 67% of children ages 3 to 20 reporting greater than 50% improvement compared with 56% of adults ages 21–40 and 44% of adults ages 41–65 reporting the same degree of improvement [33]. The treatment response was not only improved in the pediatric cohort, but response itself was age related. Given the recent data from Czarnowicki et al, this data correlates with the different T cell subsets that dominate in pediatric versus adult AD, with pediatric AD characterized by decreased T cell expression of IFN-γ and adult AD predominated by the Th22 phenotype [19].

In Hanifin's study, they also found improvement in parameters of erythema, pruritis, and excoriation in the rIFN-γ group, which were statistically significant [33]. Additionally, there were differences in edema, papulation, induration, scaling, dryness, lichenification, total clinical severity, and body surface area involvement in the treatment group; however, these differences were not statistically significant [33]. Patients also experienced improvement in other atopic symptoms of asthma, allergic rhinitis, and in particular ocular symptoms [33]. There was no statistically significant change in serum IgE levels [33]. A reduction in total serum eosinophil count was observed with a 55.3 % decrease in the treatment group (−310.96 cells/ mm^3) compared with 3.7% decrease in the placebo group (−21.06 cells/ mm^3) [33]. Along with clinical parameters, following eosinophil counts may provide clinicians with a biomarker to monitor for successful treatment response to rIFN-γ.

Since the first two clinical trials using rIFN-γ in AD, there have been 5 additional trials looking at rIFN-γ for the treatment of severe AD, with two including a pediatric population [34–38]. In all of the trials, clinical improvement was noted. The largest clinical trial of

rIFN-γ was in Korea by Jang et al looking at 51 patients with severe recalcitrant AD [34]. Patients were stratified into 3 treatment groups, a low-dose group, receiving 0.5×10^6 IU/m^2 of rIFN-γ (n=20); a high-dose group(n=21), receiving 1.5×10^6 IU/m^2 of rIFN-γ, and placebo group (n=10) for 12 weeks, and given SQ injections three times weekly [34]. Efficacy was seen in both doses of the rIFN-γ groups, as measured by 50% reduced severity, reduced erythema and pruritis, as well as improvement in loss of sleep when compared with placebo where improvement was not noted. Improvement was more rapidly observed in the high-dose group occurring within the first 6 weeks of the study, and as early as 4 weeks, though clinical results after 12 weeks were similar in both dosing groups [34].

Additionally, in the Korean study, subjects in the high dose group also had improvement in pigmentation/depigmentation, which was not observed in the low dose and placebo group [34]. Similar to previous studies, a change in total serum IgE was not observed. Unlike previous studies, no significant difference in eosinophil count was observed, and there was also no difference in CD4/CD8 subsets and ratio in the serum. The lack of eosinophil count reduction may be due to a distinct phenotype of AD present in Asians of Korean descent that has features of psoriasis, where Th17 cells tend to predominate, which play little role in eosinophil activation [39].

A statistically significant reduction was seen in CD25 positive cell infiltrates in the dermis, and EG2 binding cells. EG2 is a murine monoclonal antibody, and marker of activated eosinophils as it recognizes eosinophil cationic protein [40]. Epidermal staining of HLA-DR was also seen. Though studies have not shown any clinical relevance to HLA-DR expression in keratinocytes of patients with AD after IFN-γ treatment, its expression could serve as a marker for penetration of the rIFN-γ treatment into the epidermal layers.

The longest clinical trial of rIFN-γ for AD followed patients for 24 months [37]. Stevens et al looked at 24 patients treated with recombinant IFN-γ in a 12-week placebo-controlled trial, and transitioned them to a maintenance phase trial where they were monitored for long-term safety and efficacy [37]. In this 2-year trial, they found improvement in body surface area, clinical severity, as well as improvement in other allergic disease, which was statistically significant for allergic conjunctivitis and allergic rhinitis [37].

3.1. Side effects of subcutaneous rIFN-γ treatment

The primary side effects of rIFN-γ treatment were flu-like symptoms, transient transaminase elevation, and usually transient leukocyte, and particularly granulocyte suppression [34–38]. Flu-like symptoms included transient headache, myalgias, fever/chills, malaise, and nausea. These symptoms occurred more acutely, and diminished with long-term treatment, as well as pre-treatment with acetominophen before injection [33, 37–38] as well as timing injections to bedtime administration. One patient discontinued treatment in a short-term study, and another discontinued treatment in a long-term study due to these symptoms [33, 37]. Recombinant IFN-γ has also been noted to have suppressive effects on leukocytes, with neutropenia, and eosinopenia noted in patients [33, 36–38]. Reduction in eosinophil count appears to be a biomarker for clinical efficacy, and neutropenia is usually transient. One patient experienced persistent neutropenia during long-term study. This resolved with alternate day dosing [37]. No subjects were withdrawn from any studies due to persistent

granulocytopenia. It is interesting to note that although granuloctye counts are reduced, granulocyte function is likely improved in patients receiving treatment, as rIFN-γ is used as a treatment in Chronic Granulomatous disease to enhance neutrophil function [41–42].

In long-term study of rIFN-γ, side effects were similar to those previously mentioned, though there was one idiosyncratic report of a single patient who developed splenomegaly, which has not previously reported [37]. This study provides reassurance that treatment with rIFN-γ is not only efficacious but also safe as a long-term maintenance treatment.

4. Conclusion

The current view of AD is shifting towards categorizing patients into distinct clinical subsets, characterized by unique molecular and immune profiles. This phenotyping will need to take into account distinguishing features of the pediatric, and adult population; racial differences; as well as those with susceptibility toward cutaneous infections. IFN-γ and its down-regulation play a significant role in the pathobiology of AD, and may play a bigger role in particular subsets including infants and those with HSV and *S. aureus* colonization. Its role in AD is likely due to multiple factors, including its effect on T helper cell differentiation, as well as its immunomodulatory and antimicrobial effects. In one 2-year study, rIFN-γ was shown to reduce the number of skin infections in patients with AD requiring treatment with antibiotics, though this was not statistically significant [38]. We hypothesize rIFN-γ may be particularly useful in certain endophenotypes of AD, including the young pediatric population, who have a selective reduction of IFN-γ expression in their CLA+ skin homing T cells [19]. More studies are needed to better elucidate the occurrence of eczema herpeticum in the African American and Hispanic populations. IFN-γ expression may be a future biomarker to determine which patients will benefit from treatment. Response to IFN-γ therapy will also be dictated by IFNGR function.

Multiple studies have shown that the immune phenotype is established early in life, even younger than 6 months, with 85% of patients developing AD before one year [16–17, 43]. Prevention of AD will require early intervention in infants and young children with skin barrier creams. However, T cell modulating treatments may be needed once the AD phenotype occurs particularly in those subsets of patients complicated by recurrent viral and bacterial infections.

5. Expert Opinion: Rationale for use of rIFN-γ as Biologic Therapy in AD

AD is a chronic inflammatory skin disease, characterized by intense pruritis and eczema. Patients can undergo the atopic march leading to the development of food allergy, asthma and allergic rhinitis. This association may be due to impaired skin barrier in AD leading to systemic allergen sensitization resulting from epicutaneous absorption of food or airborne allergens. Moderate to severe AD causes significant sleep disturbance and impaired quality of life (44). Patients with severe AD do not respond optimally to topical corticosteroids or calcineurin inhibitors. This is particularly true for chronic AD complicated by recurrent skin infections with *S. aureus* or HSV, which is often associated with severe AD. Presently, severe AD that is refractory to topical steroids or calcineurin inhibitors may be treated with

systemic immunosuppressants such as cyclosporine. This can potentially increase the risk for infection as well as other systemic adverse events such as renal or kidney toxicity in this already vulnerable population.

Recent studies have revealed evidence for polarized immune activation of Th2, Th22, Th17/23 pathways in different AD subsets (1). These findings suggest that intervention with new biological agents interfering with the actions of cytokines in these pathways may be a useful strategy for intervention in treating severe AD. Support for this concept is provided by data demonstrating that treatment with a biologic therapy that interferes with IL-4/IL-13 action results in a remarkable improvement of severe AD and marked reduction in pruritus (7, 8). Data in the near future will also available for cytokine antagonism with IL22 and IL23 pathways. Treatment with IFN-γ is an immunomodulatory approach, rather than an immunosuppressive one.

Recombinant IFN-γ therapy has been tried in the past with variable responses. It is approved for use in chronic granulomatous disease where IFN-γ treatment may improve neutrophil and monocyte host defense against *S. aureus*. There was no attempt, however, in previous clinical trials to personalize rIFN-γ therapy toward AD patients expressing low IFN-γ levels. Young children and patients with AD associated with recurrent eczema herpeticum or *S. aureus* infections, have reduced IFN-γ production and or IFN-γ responses (12, 13, 29). Future studies are needed to determine if IFN-γ reduces infections in those AD subsets prone to *S. aureus* and HSV infections.

The present body of research examining the use of rIFN-γ treatment for AD focused on clinical improvement in severity of eczema rash. A precision medicine trial is required that uses low IFN-γ as a biomarker for treatment with rIFN-γ associated with infection or young children with severe AD. A critical consideration is to select the patients likely to respond optimally to IFN-γ since some patients have a functional mutation in their IFN-γ receptor that blocks pSTAT1 activation when their cells are treated with IFN-γ (31). As research in AD advances to better define endotypes as they relate to their phenotypic cluster, we will need to identify candidates with AD who would benefit from rIFN-γ over another biologic, such as an IL-4/IL-13 antagonist. Based upon recent studies, the authors hypothesize that children with severe AD may benefit more from rIFN-γ based therapy if they demonstrate a deficiency of T cell derived IFN-γ expression in their skin-homing T cells. Future studies are needed that better predict response to therapy to rIFN-γ as opposed to other biological therapies.

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Abbreviations

AD	atopic dermatitis

ADEH+	AD with history of eczema herpeticum
APC	antigen-presenting cells
EH	eczema herpeticum
HSV	herpes simplex virus
IFN-γ	interferon gamma
rIFN-γ	recombinant interferon gamma
IFNAR1	IFN-alpha receptor 1
IFNGR1	IFNγ receptor 1
IRF	interferon regulatory factor
TSLP	thymic stromal lymphopoeitin

Annotated bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. J Allergy Clin Immunol. 2014; 134:769–779. [PubMed: 25282559] •• The authors describe the shifting approach to treatment of atopic dermatitis with a comprehensive review of mechanisms involved in development of AD and identification of emerging phenotypes.
2. Leung DYM. Atopic Dermatitis: Age and race do matter! J Allergy Clin Immunol. 2015; 136:1265–1267. [PubMed: 26549637]
3. Gao PS, Rafaels NM, Hand T, et al. Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum. J Allergy Clin Immunol. 2009; 124:507–513. [PubMed: 19733298] • The authors identify that individuals with AD and filaggrin mutations are more predisposed to eczema herpeticum offering insight into why some patients with AD are more susceptible to cutaneous viral infections.
4. Cai SC, Chen H, Koh WP, et al. Filaggrin mutations are associated with recurrent skin infection in Singaporean Chinese patients with atopic dermatitis. Br J Dermatol. 2012; 166:200–203. [PubMed: 21790526]
5. van Drongelen V, Haisma EM, Out-Luiting JJ, et al. Reduced filaggrin expression is accompanied by increased Staphylococcus aureus colonization of epidermal skin models. Clin Exp Allergy. 2014; 44(12):1515–1524. [PubMed: 25352374]
6. Brauweiler AM, Bin L, Kim BE, et al. Filaggrin-dependent secretion of sphingomyelinase protects against staphylococcal α-toxin-induced keratinocyte death. J Allergy Clin Immunol. 2013; 131(2): 421–427. [PubMed: 23246020]
7. Beck LA, Thaci D, et al. Dupilumab for the treatment of adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014; 371:130–139. [PubMed: 25006719] • This is a hallmark clinical trial showing success in the treatment of moderate-to-severe AD with use of a biologic targeting the IL-4/IL-13 receptor.
8. Hamilton JD, Suárez-Fariñas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014; 134:1293–1303. [PubMed: 25482871]
9. Farrar MA, Schreiber RD. The molecular cell biology of interferon-gamma and its receptor. Annu Rev Immunol. 1993; 11:571–611. [PubMed: 8476573]

10. The International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon gamma to prevent infection in chronic gramulomatous disease. N Engl J Med. 1991; 324:509–516. [PubMed: 1846940]
11. Marciano BE, Wesley R, De Carlo ES, et al. Long-term interferon-γ therapy for patients with chronic granulomatous disease. Clin Infect Dis. 2004; 39:692–699. [PubMed: 15356785]
12. Leung DY, Gao PS, Grigoryev DN, et al. Human atopic dermatitis complicated by eczema herpeticum is associated with abnormalities in IFN-gamma response. J Allergy Clin Immunol. 2011; 127:965–973. [PubMed: 21458658] •• The authors identify decreased IFN-γ expression response as predisposing patients with AD to ADEH phenotype.
13. Machura E, Mazur B, Golemiec E, et al. Staphylococcus aureus skin colonization in atopic dermatitis children is associated with decreased IFN-gamma production by peripheral blood CD4+ and CD8+ T cells. Pediatr Allergy Immunol. 2008; 19:37–45. [PubMed: 17662038]
14. Levya-Castillo JM, et al. TSLP produced by keratinocytes promotes allergen sensitization through skin and thereby triggers atopic march in mice. J Invest Dermatol. 2013; 133:154–163. [PubMed: 22832486] • The study shows involvement of TSLP as responsible cytokine in an atopic march mouse model.
15. van der Velden VH, Laan MP, Baert MR, et al. Selective development of a strong Th2 cytokine profile in high-risk children who develop atopy: risk factors and regulatory role of IFN-gamma, IL-4 and IL-10. Clin Exp Allergy. 2001; 31:997–1006. [PubMed: 11467989]
16. Herberth G, Heinrich J, Roder S, et al. Reduced IFNgamma-and enhanced IL-4-producing CD41 cord blood T cells are associated with a higher risk for atopic dermatitis during the first 2 years of life. Pediatr Allergy Immunol. 2010; 21:5–13. [PubMed: 19552791]
17. Warner JA, Miles EA, Jones AC, et al. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? Clin Exp Allergy. 1994; 24:423–430. [PubMed: 8087653]
18. Akkoc T, de Koning PJ, Rückert B, et al. Increased activation-induced cell death of high IFN-γ–producing TH1 cells as a mechanism of TH2 predominance in atopic diseases. J Allergy Clin Immunol. 2008; 121:652–658. [PubMed: 18328893]
19. Czarnowicki T, Gonzalez J, Shemer A, et al. Severe atopic dermatitis is characterized by selective expansion of circulating T_H2/T_C2 and T_H22/T_C22, but not T_H17/T_C17, cells within the skin-homing T-cell population. J Allergy Clin Immunol. 2015; 136:104–115. [PubMed: 25748064] • The authors distinguish the pediatric and adult presentations of AD as having unique T helper cell differentiation in the skin-homing T cells.
20. Park H, Ahn K, Park MH, et al. The HLA-DRB1 polymorphism is associated with atopic dermatitis, but not egg allergy in Korean children. Allergy Asthma Immunol Res. 2012; 4:143–149. [PubMed: 22548207]
21. Giustizieri ML, Mascia F, Frezzolini A, et al. Keratinocytes from patients with atopic dermatitis and psoriasis show a distinct chemokine production profile in response to T cell-derived cytokines. J Allergy Clin Immunol. 2001; 107:871–877. [PubMed: 11344355]
22. Mathes EF, Oza V, Frieden IJ, et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. Pediatrics. 2013; 132:e149–e157. [PubMed: 23776120]
23. Seize MB, Ianhez M, Cestari Sda C. A study of the correlation between molluscum contagiosum and atopic dermatitis in children. An Bras Dermatol. 2011; 86:663–668. [PubMed: 21987130]
24. Feder HM Jr, Bennett N, Modlin JF. Atypical hand, foot, and mouth disease: a vesiculobullous eruption caused by Coxsackie virus A6. Lancet Infect Dis. 2014; 14:83–86. [PubMed: 24287184]
25. Nahmias AJ, Froeschle JE, Feorino PM, et al. Generalized eruption in a child with eczema due to coxsackievirus A16. Arch Dermatol. 1968; 97:147–148. [PubMed: 5636047]
26. Harris PN, Wang AD, Yin M, et al. Atypical hand, foot, and mouth disease: eczema coxsackium can also occur in adults. Lancet Infect Dis. 2014; 14:1043. [PubMed: 25444404]
27. Gao PS, Rafaels NM, Mu D, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. J Allergy Clin Immunol. 2010; 125:1403–1407. [PubMed: 20466416]

28. Gao PS, Leung DY, Rafaels NM, et al. Genetic variants in interferon regulatory factor 2 (IRF2) are associated with atopic dermatitis and eczema herpeticum. J Invest Dermatol. 2012; 132:650–657. [PubMed: 22113474]
29. Bin L, Edwards MG, Heiser R, et al. Identification of novel gene signatures in patients with atopic dermatitis complicated by eczema herpeticum. J Allergy Clin Immunol. 2014; 134:848–855. [PubMed: 25159465] • Using RNA-sequencing, the authors identify novel genetic signatures in the interferon regulatory pathways and Type I and III interferon genes in patients with ADEH.
30. Dorman SE, Uzel G, Roesler J, et al. Viral infections in interferon-γ receptor deficiency. J Pediatr. 1999; 135:640–643. [PubMed: 10547254]
31. Gao L, Bin L, Rafaels NM, et al. Targeted deep sequencing identifies rare loss-of-function variants in *IFNGR1* for risk of atopic dermatitis complicated by eczema herpeticum. J Allergy Clin Immunol. 2015; 136:1591–1600. [PubMed: 26343451]
32. Boguniewicz M, Jaffe HS, Izu A, et al. Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. Am J Med. 1990; 88:365–370. [PubMed: 2109531] • This is the first clinical study showing efficacy of rIFN-γ in patients with chronic severe atopic dermatitis.
33. Hanifin JM, Schneider LC, Leung DY, et al. Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol. 1993; 28:189–197. [PubMed: 8432915]
34. Jang IG, Yang JK, Lee HJ, et al. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. J Am Acad Dermatol. 2000; 42:1033–1040. [PubMed: 10827410] •• This is the largest clinical trial of rIFN-γ treatment for atopic dermatitis.
35. Reinhold U, Kukei S, Brzoska J, et al. Systemic interferon gamma treatment in severe atopic dermatitis. J Am Acad Dermatol. 1993; 29:58–63. [PubMed: 8315079]
36. Ellis CN, Stevens SR, Blok BK, et al. Interferon-γ therapy reduces blood leukocyte levels in patients with atopic dermatitis: correlation with clinical improvement. Clin Immunol. 1999; 92:49–55. [PubMed: 10413652]
37. Stevens SR, Hanifin JM, Hamilton T, et al. Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. Arch Dermatol. 1998; 134:799–804. [PubMed: 9681342]
38. Schneider LC, Baz Z, Zarcone C, et al. Long-term therapy with recombinant interferon-gamma (rIFN-γ) for atopic dermatitis. Ann Allergy Asthma Immunol. 1998; 80:263–268. [PubMed: 9532976]
39. Noda S, Suárez-Fariñas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol. 2015 Sep 28. Epub ahead of print.
40. Nakajima H, Loegering DA, Kita H, et al. Reactivity of monoclonal antibodies EG1 and EG2 with eosinophils and their granule proteins. J Leukoc Biol. 1999; 66:447–454. [PubMed: 10496315]
41. Sechler JM, Malech HL, White CJ, et al. Recombinant human interferon-gamma reconstitutes defective phagocyte function in patients with chronic granulomatous disease of childhood. Proc Natl Acad Sci U S A. 1988; 85:4874–4878. [PubMed: 2838849]
42. Ezekowitz RA, Orkin SH, Newburger PE. Recombinant interferon gamma augments phagocyte superoxide production and X-chronic granulomatous disease gene expression in X-linked variant chronic granulomatous disease. J Clin Invest. 1987; 80:1009–1016. [PubMed: 2821069]
43. Tang ML, Kemp AS, Thorburn J, et al. Reduced interferon-gamma secretion in neonates and subsequent atopy. Lancet. 1994; 344:983–985. [PubMed: 7934430]
44. Fishbein AB, Vitaterna O, Haugh IM, et al. Nocturnal eczema: Review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. J Allergy Clin Immunol. 2015; 136:1170–1177. [PubMed: 26549635] •• An excellent review on sleep disturbance in atopic dermatitis.

Highlights

- Reduced interferon gamma (IFN-γ) expression plays a role in the development of atopic dermatitis.
- Recombinant interferon gamma therapy may be considered as treatment in patients with moderate to severe atopic dermatitis
- Recombinant interferon gamma therapy is used in chronic granulomatous disease to enhance neutrophil function against organisms, such as *Staphylococcus aureus*.
- Interferon gamma therapy may be considered in those with AD with predisposition towards infections with *staphylococcus aureus* or herpes simplex virus.
- Interferon gamma therapy may benefit young children with AD as they have reduced expression of IFN-γ.