Clin Exp Med
DOI 10.1007/s10238-011-0164-3

ORIGINAL ARTICLE

Recombinant human interferon gamma (Gamma Immunex) in treatment of atopic dermatitis

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Received: 8 June 2011 / Accepted: 28 October 2011

Abstract Atopic dermatitis (AD) is a chronic, inflammatory skin disease which is characterized by severe pruritus and affects patients' quality of life. In recent years gamma interferon (IFN-gamma) has been accepted as a novel treatment for severe AD, however, its mechanism of action is not clearly identified. Present study evaluated the effect of recombinant human interferon gamma (rIFN-gamma: Gamma Immunex, Exir Pharmaceutical Company, Iran) on severity of AD (SCORAD), dermatology life quality index (DLQI) as well as serum levels of IL-4, IgE and IL-6 in AD patients. Twenty AD patients were entered in to a study in Baqiyatallah outpatient clinics and received rIFN-gamma (50 μg/m^2 body area, 3 times per week, subcutaneously) for 1 month. SCORAD and DLQI were assessed at beginning and end of the treatment period. IL-4, IL-6 and IgE were measured in blood samples before and after 1 month treatment with rIFN-gamma. DLQI mean value before treatment was 20.80 ± 3.95, which decreased to 8.20 ± 2.14 after treatment ($P < 0.001$). SCORAD-A (percentile of the body surface involved in AD), SCORAD-B (the severity of clinical features) and SCORAD-C (patients' scaling of itching and somnolence) significantly decreased after treatment ($P < 0.001$, $P < 0.001$ and $P < 0.01$). Total SCORAD at the end of treatment period was less than basal value (27.83 ± 8.48 vs. 70.04 ± 8.48; $P < 0.001$). Treatment with rIFN-gamma decreased serum levels of IL-4 and IL-6 ($P < 0.05$), but IgE remained unchanged. Results suggested the controlling effect of rIFN-gamma treatment on clinical symptoms of AD, which involves suppression of IL-4 but not IgE production.

Keywords Atopic dermatitis · Gamma interferon · Quality of life · Interleukin

Introduction

Atopic dermatitis (AD) as the cutaneous manifestation of atopy [1] is a chronic, relapsing, inflammatory skin disease characterized by highly pruritic and eczematous skin lesions [2]. This common condition [1, 2] affects quality of life of patients and families in a significant manner. These patients evidence eosinophilia and a hyper-IgE state. Various treatment strategies have been used for management of AD but there is no standard curative therapy for treatment of the disease and it is still one of the challenges of dermatology. Topical and systemic corticosteroids have been used as treatment modalities. Oral administration of antihistamines, both old and new generation, is reported to be useful [3]. Leukotriene antagonists [4], immunosuppressive therapy with cyclosporine [5], azathioprine [6], mycophenolate [7] and tacrolimus [8] are other treatment options. Side effects of these treatments limit their clinical administration. In recent years efficacy and safety of gamma interferon have been studied and IFN-gamma is now accepted as a novel treatment for severe AD patients [9–11].

Immunologic factors of pathogenesis: The Th1 cells mediate the production of interleukin 2 (IL-2), IFN-gamma and tumor necrosis factor (TNF), activating the macrophages and promoting delayed hypersensitivity reactions.

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Published online: 19 November 2011

The Th2 cells release IL-4, IL-5, IL-6 and IL-10, which activate the B cells [1]. The complex and complicated immunologic mechanisms involved in pathogenesis of AD is not completely understood but we know that in the case of AD there is an imbalance between Th1 and Th2 cells, the Th2 cells predominates and mononuclear cells produce increased levels of TH2 cytokines. Consequently, there is increased production of IL-4 and also abnormally low levels of IFN-gamma [12–14]. IL-4 induces isotype switching to IgE synthesis and stimulates the production of IgE [15–17]. Mechanism of action of IFN-gamma in treatment of AD is not clearly identified but it is thought to downregulate the activity of interleukin-4- and interleukin-5-producing T helper 2 cells [10, 18]. IFN-gamma gene transfer in mice was associated with reduced production of IgE and inhibition of mRNA expression of IL-4, IL-5, IL-10, IL-13 and IL-17 [19], whereas in most human studies IFN-gamma could not decrease the IgE production [10, 13, 20].

In this study we evaluated the effect of rIFN-gamma (Gamma Immunex) on the severity of AD, life quality of patients as well as serum levels of IL-4 as a modulator of IgE production and IL-6 as a pre-inflammatory factor in AD patients.

Materials and methods

This clinical trial was carried out in Baqiyatallah outpatient clinics (Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, Tehran, Iran) from July 2010 until April 2011. The Ethics Committee of Baqiyatallah University of Medical Sciences approved the protocol of the study.

AD patients diagnosed clinically based on UK Working Party's Diagnostic Criteria [21], which has been validated in several studies. Its sensitivity and specificity was 80 and 97%, respectively, and positive and negative predictive values were 80 and 97%, respectively [22]. Acceptable repeatability has been demonstrated for the six features contained within the UK criteria [23].

Only AD patients without any contraindication for administration of IFN-gamma were offered the opportunity to enroll in the trial and all took informed consent. Patients who had previous history of treatment with IFN-gamma 4 months ago, renal and hepatic disease, depression, epilepsy, history of blood pressure, and patients with respiratory system defects, cardiovascular and immune disease and diabetic subjects, were excluded from study. All patients were subjected to thorough history taking, and general and dermatological examination. Severity of the disease was assessed in all patients by means of the SCORAD index. Blood sampling was done and 5 ml of blood from every subject left to clot, centrifuged and serum was stored at −20°C until quantitative assay of IL-4 and IL-6 and IgE was done. We used Quantikine colorimetric sandwich ELISA immunoassay kits (R&D Diagnostic Minneapolis, USA) for quantitative assessment of serum levels of the interleukins and IgE and concentrations were expressed in pg/ml. Subjects were educated to receive self-administered 50 $\mu g/m^2$ of subcutaneous recombinant human interferon gamma (rIFN-gamma: Gamma Immunex, Exir Pharmaceutical Company, Tehran, Iran) as the optimal dose three times a week for 1 month [24]. All subjects were told to report any side effect of the treatment and abstain from any allergen and worsening factors as well as they could.

SCORAD scoring system [25, 26]

Index of SCORAD (SCORe of AD) consists of three parts. The A part, ranging from 0 to 100, refers to the percentile of the body surface involved in disease. The B part demonstrates the severity of the disease by means of grading 6 signs and symptoms of the disease from 0 to 3. These signs and symptoms include erythema, edema and papulation, excoriation, lichenification, crust and excretion, and skin dryness. Maximum score of the B part is 18. Ultimately, the C part is a subjective scale of daily itching and somnolence, each of them ranging from 0 to 10, to reach a maximum total score of 20. Total SCORAD is calculated with this equation: $\text{SCORAD} = \text{A}/5 + 7\text{B}/2 + \text{C}$. The higher score the more severe disease.

Dermatology life quality index (DLQI) [27]

DLQI is a questionnaire consisting of 10 questions about life quality of the patient. Score of every question ranges from 0 to 3 to reach a maximum score of 30 which demonstrates the worst life quality.

Statistical analysis

At the end of the treatment period another blood sampling was done and the patients' laboratory and clinical features before and after treatment were compared using SPSS 17 software. Kolmogorov–Smirnov test was used for evaluation of normal distribution for each of the variables. Wilcoxon signed-rank test was applied to compare changes in values. Statistical significance was recognized at $P < 0.05$.

Results

Twenty eligible patients participated in this study: 10 males (50%) and 10 females (50%). Mean age was 38.9 ± 10.96 years (range 21–65 years).

Clinical features

Mean duration of disease in the patients was 4 ± 1.3 years. Hands were involved in 85% of the patients, arms in 65%, and abdomen in 55% of them. 30% of the patients had generalized lesions. Lichenification in flexor areas was present in 60% of the cases.

DLQI and SCORAD

DLQI mean value before treatment (DLQI-1) was 20.80, which decreased to 8.20 after treatment (DLQI-2). These data showed that the effect of treatment with rIFN-gamma on improving patients' quality of life was significant ($P < 0.001$; Table 1).

SCORAD-A index, which shows the percentile of the body surface involved in AD, significantly decreased after treatment and reached 29.05 ± 16.40% from 68.57 ± 20.00 at the beginning of study ($P < 0.001$; Table 1).

SCORAD-B index, which shows the severity of clinical features, was also decreased significantly ($P < 0.01$). The mean value for SCORAD-B before rIFN-gamma treatment was 11.35 ± 1.49 and after treatment was 4.55 ± 1.50 (Table 1).

SCORAD-C, which shows patients scaling of itching and somnolence, was 16.60 at the beginning of study (SCORAD-C1) which was decreased by rIFN-gamma treatment to 6.10 ($P < 0.01$; Table 1).

At the end of treatment period with rIFN-gamma, total SCORAD had been decreased compared to the basal value 70.04 ± 8.48 (27.83 ± 8.48; $P < 0.001$; Table 1).

Laboratory tests

Eosinophil count

Treatment with rIFN-gamma decreased mean eosinophil count from 2.40 (before treatment) to 2.25 (after treatment), but it was not statistically significant ($P = 0.074$; Table 2).

Table 1 Dermatology life quality index (DLQI) and SCORAD scoring data before and after treatment

	Min	Max	Mean	SD	*P* value
DLQI-1	8	27	20.80	3.95	<0.001
DLQI-2	4	11	8.20	2.14	
SCORAD-A1	32.50	100	68.57	20.00	<0.001
SCORAD-A2	5.50	58.00	29.05	16.40	
SCORAD-B1	9	15	11.35	1.49	<0.01
SCORAD-B2	3	8	4.55	1.50	
SCORAD-C1	7	20	16.60	4.62	<0.01
SCORAD-C2	0	11	6.10	3.12	
SCORAD-1	60	85.30	70.04	8.48	<0.001
SCORAD-2	17.30	47.00	27.83	8.48	

In each set of variables, 1 = before treatment and 2 = after treatment

Wilcoxon signed-rank test was applied to compare changes in values

IgE

There was a slight increase in mean serum IgE level of the patients after treatment. Mean IgE level before treatment was 33.82 meanwhile after treatment was 34.55. The increase was not statistically significant ($P = 0.092$; Table 2).

IL-4 and IL-6

Treatment with rIFN-gamma decreased mean serum IL-4 and IL-6 levels from 23.47 ± 3.58 and 10.46 ± 1.69 at the beginning of study to 13.22 ± 1.34 and 5.03 ± 1.00 at the end of study, respectively ($P < 0.012$ and $P < 0.024$, respectively; Table 2).

Discussion

Atopic dermatitis is a chronic, relapsing, inflammatory skin disease that is characterized by highly pruritic and eczematous skin lesions which greatly affects life quality of patients. It seems that an imbalance between activity of Th1 and Th2 cells causes eosinophilia and increased production of IgE. Th2 cytokines such as IL-4 which is associated with the increase in IgE production and IL-6 which is a pre-inflammatory factor are involved in pathogenesis. There are several therapeutic choices but there is no standard curative strategy. IFN-gamma has been recently used for treatment of AD. Its mechanism of action is not yet completely identified but the beneficial effects of IFN-gamma have been attributed mainly to an immunomodulating effect on the expression of certain immunologic markers and suppression of activity of Th2 cells. We assessed the effect of rIFN-gamma (Gamma Immunex) on

Table 2 Experimental finding in serum of patients before and after treatment with INF-gamma

	Min	Max	Mean	SD	*P* value
Eosinophil before	0.2	6.3	2.40	2.34	0.074
Eosinophil after	0.2	6.3	2.25	2.49	
IgE before	31.4	37.3	33.82	1.80	0.092
IgE	30.70	38.40	34.55	2.02	
IL-4 before	17.5	28.5	23.47	3.58	<0.012
IL-4 after	10.3	15.1	13.22	1.34	
IL-6 before	8.5	14.4	10.46	1.69	<0.024
IL-6 after	3.8	7.9	5.03	1.00	

Wilcoxon signed-rank test was applied to compare changes in values

severity and extent of AD, quality of life of patients, and serum levels of IgE, IL-4 and IL-6 as well as eosinophil count in 20 patients with AD.

IFN-gamma could improve life quality of our patients in a significant manner. Mean DLQI before treatment was 20.80 ± 3.95 (range 8–27) which was decreased to 8.20 ± 2.14 (range 4–11) after treatment. Furthermore, extent of disease (SCORAD-A) and severity of clinical signs and symptoms (SCORAD-B and SCORAD-C) were decreased. Clinical improvement of AD patients with rIFN-gamma in this study is consistent with the previous ones, as preceding studies had revealed beneficial effects of IFN-gamma on clinical measures of AD patients [11, 27–29]. Musial et al. reported marked clinical improvement starting from the third week of treatment with IFN-gamma [9]. Jang et al. [10] along with Reinhold et al. [20] showed the same results.

There are different and controversial reports about the effect of IFN-gamma on IgE and peripheral blood eosinophil counts in AD patients. Schneider et al. [28] reported that IFN-gamma could improve the clinical symptoms of patients but their serum IgE levels were not decreased. Steven et al. [29] reported clinical improvement and decreased eosinophil count but a nonsignificant increase in IgE level after treatment with recombinant IFN-gamma. Patients' symptoms of Musial et al. were improved, serum IgE levels were unchanged and eosinophil count decreased only transiently [30]. Chang and Stevens in a literature review demonstrated that treatment with recombinant IFN-gamma did not lower serum IgE levels; instead, decreases were noted in absolute white blood cell and eosinophil counts that tended to correlate with clinical improvement [12]. In our study mean eosinophil count was decreased from 2.40 (before treatment) to 2.25 (after treatment), but was not significant. Meanwhile, there was also a slight and nonsignificant increase in mean serum IgE level of the patients after treatment from 33.82 to 34.55. In addition, administration of rIFN-gamma caused a significant decrease in serum levels of IL-4 and IL-6.

Mechanism of action of IFN-gamma in treatment of AD patients is not completely clear. Evidences show that decreased IFN-gamma and increased IL-4 production in atopic dermatitis promotes IgE synthesis and administration of anti-IFN-gamma receptor antibody, which blocks cellular binding of IFN-gamma, causes an increase in capacity to induce IgE synthesis [13]. IL-4 induces IgE production in peripheral blood mononuclear cells of healthy persons and AD patients [15]. Gruner et al. showed IL-4 stimulates IgE production in vitro in B cells of children with atopic dermatitis [16] and Sato et al. showed that in AD patients with higher IgE levels, IL-4 expression after in vitro stimulation is more than patients with lower IgE levels [17]. Therefore, IL-4 plays a significant role in the production of IgE. Hattori et al. reported that IFN-gamma gene transfer in mice models of AD was associated with reduced production of IgE and inhibition of mRNA expression of IL-4 [19]. In addition, IFN-gamma in an in vitro setup prevented the stimulation of IgE synthesis induced by IL-4 [16].

However, there are some controversial reports suggesting that suppression of Th2 cytokines in mice may not completely prevent dermatitis and even hyperproduction of IFN-gamma may play a role in developing dermatitis [31]. Another report suggested that when circulating T cells are stimulated under antigen presenting cell-independent conditions, AD is not characterized by the shift in the reciprocal relationship between IL-4 and IFN-gamma production, which has been postulated to explain the pathogenesis of IgE elevation and the therapeutic action of IFN-gamma in patients with atopic dermatitis [32].

Our findings suggested that rIFN-gamma can decrease IL-4 serum level but it cannot decrease IgE serum level and eosinophil count. Although IL-4 has an important role in modulating the IgE production, decrease in serum IL-4 did not affect IgE production, while clinical features of the patients were improved. It seems that IL-4 is involved in modulating the severity of AD symptoms, but not by means of IgE production. Also, the role of IL-6 in AD and effect of IFN-gamma on its' level, has not been focused. The results of present study showed that IFN-gamma could decrease the serum IL-6 along with IL-4, suggesting that IFN-gamma can cause marked clinical improvement in AD patients and IL-4 and IL-6 are two therapeutic targets in mechanism of action of IFN-gamma. More studies are required to completely identify the immunological markers and their complex relationship involved in pathogenesis of AD and treatment with IFN-gamma. In addition to that, our study was an open clinical trial and conducting case–control studies with more patients for further investigations in future is necessary.

Acknowledgments The authors are thankful to Department of Internal Medicine, Baqiyatallah University of Medical Sciences, for providing experimental measurements and instrumental supports.

Conflict of interest All funds for this study were from the Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, and there was no conflict of interest to other institutes. The authors alone are responsible for the content and writing of the paper.

References

1. Wasserbauer N, Ballow M (2010) Atopic dermatitis. Am J Med 122(2):121–125
2. Dou YC, Hagstromer L, Emtestam L, Johansson O (2006) Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. Arch Dermatol Res 298:31–37

3. Herman SM, Vender RB (2003) Antihistamines in the treatment of dermatitis. J Cutan Med Surg 7(6):467–473
4. Broshtilova V, Gantcheva M (2010) Therapeutic hotline: cysteinyl leukotriene receptor antagonist montelukast in the treatment of atopic dermatitis. Dermatol Ther 23(1):90–93
5. Haw S, Shin MK, Haw CR (2010) The efficacy and safety of long-term oral cyclosporine treatment for patients with atopic dermatitis. Ann Dermatol 22(1):9–15
6. Hughes R, Collins P, Rogers S (2008) Further experience of using azathioprine in the treatment of severe atopic dermatitis. Clin Exp Dermatol 33(6):710–711
7. Murray ML, Cohen JB (2007) Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. Clin Exp Dermatol 32(1):23–27
8. Fleischer AB Jr, Boguniewicz M (2010) An approach to pruritus in atopic dermatitis: a critical systematic review of the tacrolimus ointment literature. J Drugs Dermatol 9(5):488–498
9. Musiał J, Milewski M, Undas A, Kopiński P, Duplaga M, Szczeklik A (1994) Human recombinant interferon gamma in the treatment of atopic dermatitis. Pol Arch Med Wewn 92(6):499–506
10. Jang IG, Yang JK, Lee HJ, Yi JY, Kim HO, Kim CW, Kim TY (2000) Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. J Am Acad Dermatol 42(6):1033–1040
11. Hanifin JM, Schneider LC, Leung DYM et al (1993) Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol 28:189–197
12. Chang TT, Stevens SR (2002) Atopic dermatitis: the role of recombinant interferon-gamma therapy. Am J Clin Dermatol 3(3):175–183
13. Jujo K, Renz H, Abe J, Gelfand EW, Leung DY (1992) Decreased interferon gamma and increased interleukin-4 production in atopic dermatitis promotes IgE synthesis. J Allergy Clin Immunol 90(3 Pt 1):323–331
14. Tenda Y, Yamashita M, Kimura MY, Hasegawa A, Shimizu C, Kitajima M, Onodera A, Suzuki A, Seki N, Nakayama T (2006) Hyperresponsive TH2 cells with enhanced nuclear factor-kappa B activation induce atopic dermatitis-like skin lesions in Nishikinezumi Cinnamon/Nagoya mice. J Allergy Clin Immunol 118(3):725–733
15. Punnonen J, Punnonen K, Jansén CT, Kalimo K (1993) Interferon (IFN)-alpha, IFN-gamma, interleukin (IL)-2, and arachidonic acid metabolites modulate IL-4-induced IgE synthesis similarly in healthy persons and in atopic dermatitis patients. Allergy 48(3):189–195
16. Gruner S, Liebenthal C, Heusser C, Brinkmann V, Zwirner A, Reinicke C, Harnack K, Sönnichsen N, Volk HD (1991) The influence of interferon-gamma and interleukin-4 on IgE production in B lymphocytes of patients with atopic dermatitis. A possible criterion for selection of patients for interferon therapy. Acta Derm Venereol 71(6):484–487
17. Sato A, Tsuji K, Yamamura M, Morita Y, Kanzaki H, Tada J, Makino H, Arata J (1998) Increased type 2 cytokine expression by both CD4 + CD45RO + T cells and CD8 + CD45RO + T cells in blood circulation is associated with high serum IgE but not with atopic dermatitis. J Invest Dermatol 111(6):1079–1084
18. Shibata S, Maeda S, Kondo N, Inoue A, Maeda S, Chimura N, Fukata T (2011) Effect of recombinant canine interferon-γ on granulocyte-macrophage colony-stimulating factor, transforming growth factor-β and CC chemokine ligand 17 mRNA transcription in a canine keratinocyte cell line (CPEK). Vet Dermatol 22(1):24–30
19. Hattori K, Nishikawa M, Watcharanurak K, Ikoma A, Kabashima K, Toyota H, Takahashi Y, Takahashi R, Watanabe Y, Takakura Y (2010) Sustained exogenous expression of therapeutic levels of IFN-gamma ameliorates atopic dermatitis in NC/Nga mice via Th1 polarization. J Immunol 184(5):2729–2735
20. Reinhold U, Kukel S, Brzoska J, Kreysel HW (1993) Systemic interferon gamma treatment in severe atopic dermatitis. J Am Acad Dermatol 29(1):58–63
21. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ (1994) The U.K. working partýs diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 131:383–396
22. Williams HC, Burney PGJ, Pembroke AC, Hay RJ (1994) The UK working party's diagnostic criteria for atopic dermatitis III: Independent hospital validation. Br J Dermatol 131:406–416
23. Williams HC, Burney PGJ, Strachan D, Hay RJ (1994) The UK working party's diagnostic criteria for atopic dermatitis II: observer variation of clinical diagnosis and signs of atopic dermatitis. Br J Dermatol 131:397–405
24. Boguniewicz M, Jaffe HS, Izu A et al (1990) Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. Am J Med 88:365–370
25. Costa C, Rilliet A, Nicolet M, Saurat JH (1989) Scoring atopic dermatitis. The simpler the better? Acta Derm Venereol(Stockh) 69:41–45
26. Oranje AP, Glazenburg EJ, Wolkerstorfer A, De Waard-Van Der Spek FB (2007) Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol 157:645–648
27. Finlay A, Khan G (1994) Dermatology life quality index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 19:210–216
28. Schneider LC, Baz Z, Zarcone C, Zurakowski D (1998) Long term therapy with recombinant interferon-gamma for atopic dermatitis. Ann Allergy Asthma Immunol 80:263–268
29. Steven SR, Hanifin JM, Hamilton T, Tofte SJ, Cooper KD (1998) Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. Arch Dermatol 134:799–804
30. Musial J, Milewski M, Undas A, Kopinski P, Duplaga M, Szczeklik A (1995) Interferon-gamma in treatment of atopic dermatitis: influence on T-cell activation. Allergy 50:520–523
31. Takakura M, Takeshita F, Aihara M, Xin KQ, Ichino M, Okuda K, Ikezawa Z (2005) Hyperproduction of IFN-gamma by CpG oligodeoxynucleotide-induced exacerbation of atopic dermatitis-like skin lesion in some NC/Nga mice. J Invest Dermatol 125(6):1156–1162
32. Simon MR, Cooper KD, Norris RB, Blok B, King CL (1995) Antigen presenting cell-independent cytokine and spontaneous in vitro IgE production in patients with atopic dermatitis: increased interferon-gamma production and lack of effects of in vivo low-dose interferon-gamma treatment. J Allergy Clin Immunol 96(1):84–91