Serum Interferon-γ Is a Psoriasis Severity and Prognostic Marker

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The aim of this study was to measure serum interferon-γ (IFN-γ) levels in participants with different types and severities of psoriasis. The study was conducted on 21 participants with psoriasis. Participants were divided into 3 groups according to disease severity: erythrodermic, severe plaque, and mild to moderate plaque psoriasis. Fifteen participants received different treatment modalities for 16 weeks and were followed for an additional 12 weeks. The enzyme-linked immunosorbent assay technique was used to measure serum IFN-γ levels in participants before treatment and compared with matched controls and participants receiving treatment. Significant differences were detected between participants and controls in mean serum IFN-γ levels before treatment ($P<.05$). There was a positive correlation between serum IFN-γ levels and psoriasis area and severity index (PASI) scores, and between serum IFN-γ levels and clinical type of psoriasis, with the highest serum IFN-γ levels in the erythrodermic psoriasis group and the lowest in the mild to moderate plaque psoriasis group. Irrespective of the type of treatment, 13 of 15 participants who showed improvement in disease condition with a significant decrease in PASI scores also had a significant decrease in serum IFN-γ levels ($P<.05$). Moreover, participants with serum IFN-γ levels that did not dramatically decrease had a shorter remission period compared with those who showed a significant decrease in serum IFN-γ levels. The substantial elevation and variation in serum IFN-γ levels according to disease severity suggest that IFN-γ has a role in determining disease severity and therapy evaluation, which encourages further research on anti–IFN-γ biologic therapy in the treatment of psoriasis.

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Interferon-γ (IFN-γ), a helper T cell 1 (T_H1)–derived cytokine, is an important immune regulator and plays a major role in the pathogenesis of psoriasis. Interferon-γ influences cell differentiation of the progenitor helper T cells T_H0 and T_H1, and inhibits differentiation into T_H2 cells. It is capable of inducing the expression of intercellular adhesion molecule 1 (ICAM-1) and HLA-DR, thus mediating interactions between inflammatory T cells and keratinocytes facilitating T cell migration to lesional epidermis.[1,2] Moreover, it induces antiapoptotic protein BCLx and alters the expression of the apoptotic catalytic enzymes cathepsin D and zinc-alpha-2-glycoprotein in psoriatic skin, thus promoting keratinocyte proliferation.[1,3] Interferon-γ also enhances CD1d expression on keratinocytes, which plays a central role in the development and activation of natural killer T cells.[4] Prior studies reported an increase in serum IFN-γ levels in patients with psoriasis.[5,6]

To evaluate the role of IFN-γ in psoriasis prognosis, the current study measured serum IFN-γ levels in participants with erythrodermic, severe plaque, and mild to moderate plaque psoriasis. The correlation of these results with the psoriasis area and severity index (PASI) score and clinical type of psoriasis also was evaluated. In addition, we assessed participants who responded to treatment and compared serum IFN-γ levels with disease outcome.

Methods

The study was conducted on 21 participants with psoriasis and 15 matched controls from the Department of Dermatology, Ain Shams University, and the

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National Research Centre, both in Cairo, Egypt (January–July 2005). Each participant consented to the use of residual blood samples from a routine laboratory draw to measure serum IFN-γ levels.

Participants were chosen and divided into 3 groups according to disease severity: (1) erythrodermic psoriasis; (2) severe plaque psoriasis (body surface area involvement >20%); and (3) mild to moderate plaque psoriasis (body surface area involvement ≤20%). The PASI score also was calculated (0=no disease; 72=maximal disease).

Fifteen participants (5 with erythrodermic psoriasis, 7 with severe plaque psoriasis, 3 with mild to moderate plaque psoriasis) received different treatment modalities (4 methotrexate, 2 cyclosporin A, 3 narrowband-UVB [NB-UVB], 3 psoralen plus UVA [PUVA], 3 topical calcipotriene) for 16 weeks, and then another blood sample was drawn. These participants were followed for an

additional 12 weeks. Serum IFN-γ levels were measured in all participants before treatment using the enzyme-linked immunosorbent assay technique and compared with controls and participants receiving treatment.[6]

Statistical analysis of the data was performed using SPSS Version 12.

Results

The study included 11 females (52.4%) and 10 males (47.6%) with a mean age (standard deviation) of 35 (10.7) years and a mean disease duration of 8.9 years. Six participants had erythrodermic psoriasis, 9 had severe plaque psoriasis, and 6 had mild to moderate plaque psoriasis. Psoriasis area and severity index scores before treatment ranged from 2.4 to 63.3, with a mean (standard deviation) of 25.8 (15.1)(Table). A statistically significant difference was observed comparing PASI scores of

PASI and IFN-γ Participant and Control Group Data

Parameter Measured	Total Participants (N=21)	Erythrodermic Psoriasis Group (n=6)	Severe Plaque Psoriasis Group (n=9)	Mild to Moderate Plaque Psoriasis Group (n=6)	Control Group (n=15)
PASI before treatment					
Mean (SD)	25.8 (15.1)	44.1 (12.0)[a,b]	23.9 (5.3)[a,b]	10.4 (5.3)[a,b]	N/A
Median	22.4	40.5	22.4	10.4	N/A
PASI after treatment[c]					
Mean (SD)	8.9 (6.6)[a,d]	11.6 (5.9)	9.8 (6.8)	2.0 (0.5)	N/A
Median	7.2	8.6[a,d]	8.1[a,d]	2.2	N/A
IFN-γ before treatment, pg/mL					
Mean (SD)	999.2 (831.8)[a,e]	1755.2 (795.6)	862.5 (663.1)	448.1 (589.0)	6.8 (1.7)[a,e]
Median	1796.0	1437.5[a,e]	722.7[a,e]	109.2[a,e]	7.4
IFN-γ after treatment, pg/mL[c]					
Mean (SD)	106.5 (152.9)[a,f]	139.5 (176.4)	116.1 (172.6)	29.2 (1.2)	N/A
Median	32.4	87.4[a,f]	32.4[a,f]	29.6	N/A

Abbreviations: PASI, psoriasis area and severity index; IFN-γ, interferon-γ; SD, standard deviation; N/A, not applicable.
[a]$P<.05$.
[b]Comparing PASI score between psoriasis subtypes before treatment.
[c]Fifteen participants received treatment (5 with erythrodermic psoriasis, 7 with severe plaque psoriasis, and 3 with mild to moderate plaque psoriasis).
[d]Comparing PASI score before and after treatment.
[e]Comparing IFN-γ levels before treatment.
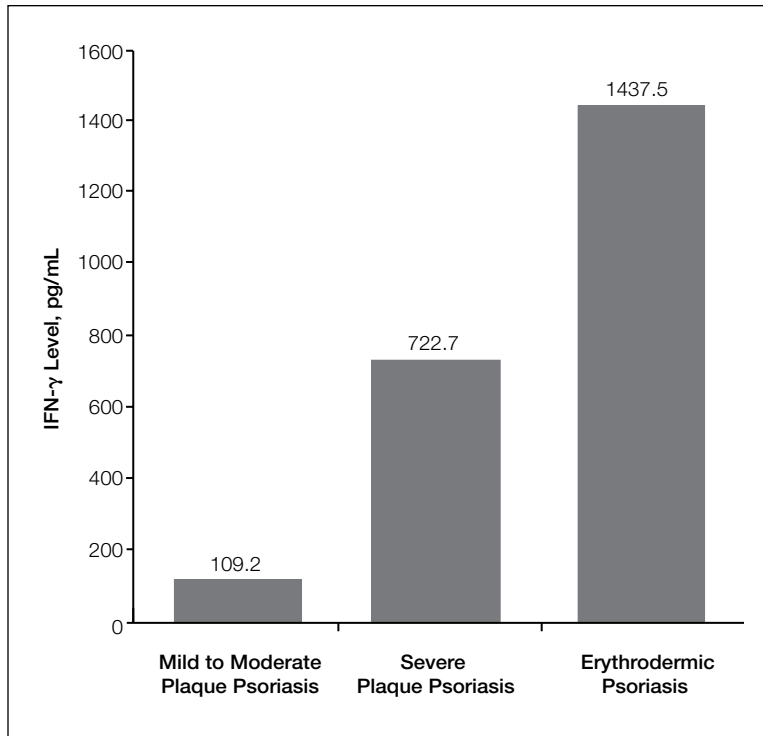[f]Comparing IFN-γ levels before and after treatment.

Figure 1. Median serum interferon-γ (IFN-γ) levels before treatment in participants with mild to moderate plaque psoriasis (n=6), severe plaque psoriasis (n=9), and erythrodermic psoriasis (n=6).

participants in the erythrodermic psoriasis group with the severe plaque psoriasis group or mild to moderate plaque psoriasis group ($P<.05$). Significant differences were detected between participants and controls in mean serum IFN-γ levels before treatment ($P<.05$). The highest median serum IFN-γ level before treatment was observed in participants with erythrodermic psoriasis, showing a statistically significant difference compared with the other 2 groups ($P<.05$). Furthermore, serum IFN-γ levels in the severe plaque psoriasis group were statistically higher before treatment than mild to moderate plaque psoriasis (Figure 1). There was a positive correlation between serum IFN-γ levels and PASI scores (Pearson $r=0.56$; $P<.01$), and between serum IFN-γ levels and clinical type of psoriasis (Pearson $r=0.61$; $P<.01$)(Figure 2).

Fifteen participants received different treatment modalities in our inpatient department. Another blood sample was drawn from each participant after 16 weeks of treatment. Treatment modalities varied according to the participants' general condition and disease severity. Participants with erythrodermic psoriasis received either methotrexate or cyclosporin A; participants with severe plaque psoriasis received methotrexate, cyclosporin A, or UV therapy (NB-UVB or PUVA); and participants with mild to moderate plaque psoriasis received topical calcipotriene. Irrespective of the type of treatment, 13 of 15 participants who showed improvement in disease condition with a significant

decrease in PASI scores (9 participants achieved PASI 75; 4 participants achieved PASI 50) also had a significant decrease in serum IFN-γ levels ($P<.05$). A significant difference was found in the median serum IFN-γ levels before and after treatment in the erythrodermic psoriasis group as well as the severe plaque psoriasis group ($P<.05$)(Table). Moreover, participants with serum IFN-γ levels that did not dramatically decrease had a shorter remission period (≤12 weeks) compared with those who showed a significant decrease in serum IFN-γ levels (>12 weeks; participants were followed after the end of the study).

Comment

Interferon-γ currently is considered a key cytokine in the pathogenesis of psoriasis,[6-8] which was clinically proven when treatment with recombinant human interferon gamma administered subcutaneously proved ineffective in psoriatic arthritis, and approximately 25% of treated participants (10/42) developed foci of psoriasis at the injection sites.[9] This reaction did not occur at the sites of saline injection, implying that the lesions did not develop because of Köbner phenomenon.[10] In psoriatic lesions, considerable amounts of IFN-γ–positive cells were detected in the papillary dermis and epidermis. Interferon-γ staining was considered to be highly specific because it could be completely blocked by preabsorption with recombinant interferon gamma.[11]
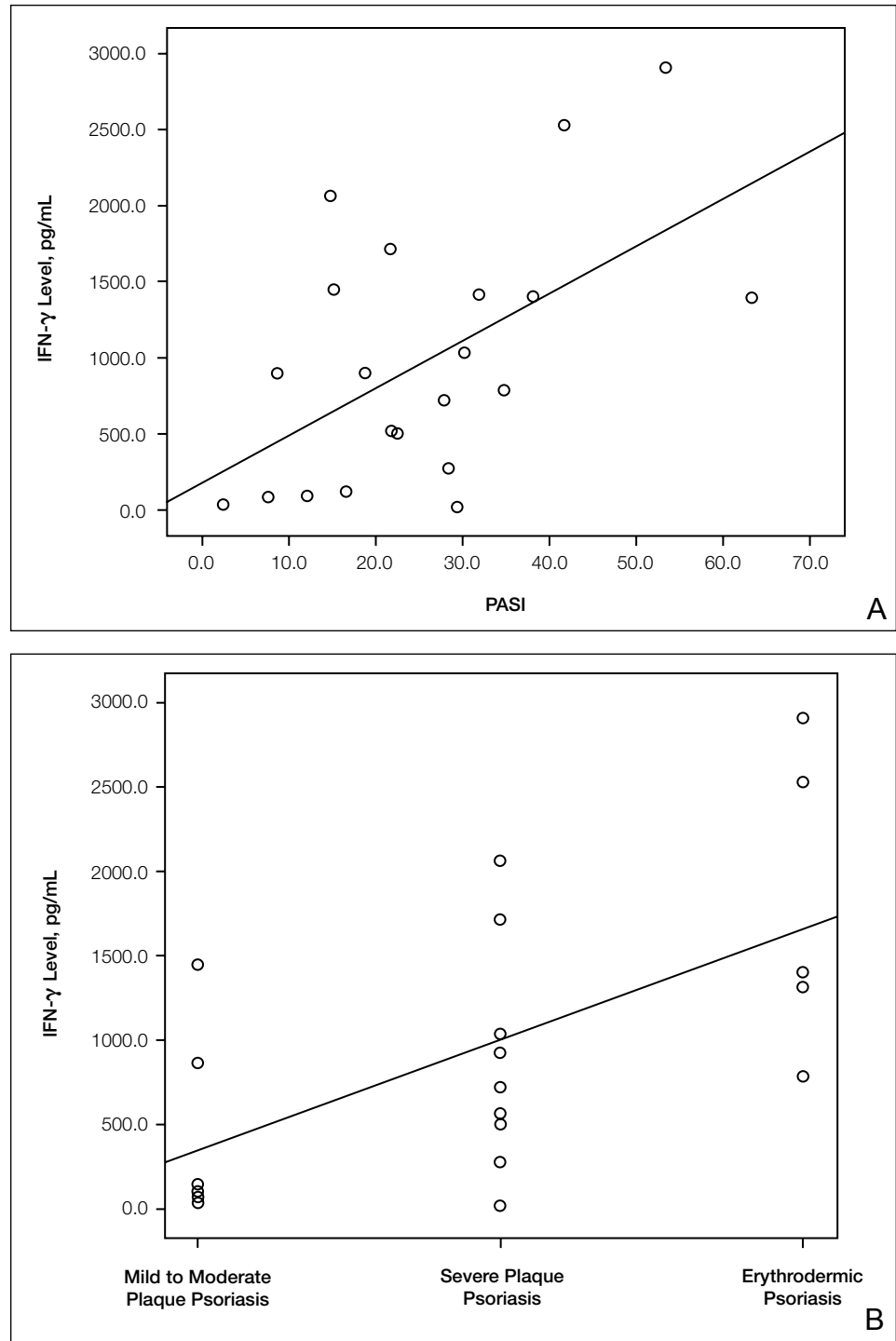
Figure 2. There was a positive correlation between serum interferon-γ (IFN-γ) levels and psoriasis area and severity index (PASI) scores (A), and between serum IFN-γ levels and clinical type of psoriasis (B).

Cytokines act in an interrelated immune cascade, with IFN-γ playing a central role. It stimulates the release of a number of cytokines, such as IL-1, IL-6, IL-8, tumor necrosis factor α, and inflammatory mediators,[7] in addition to inducing the expression of ICAM-1, HLA-DR, and vascular CAM 1 on keratinocytes and endothelial cells, thereby attracting lymphocytes from the circulation.[1,2,12] Hong et al[13] suggested that IFN-γ mainly is concerned with the promotion of keratinocyte proliferation, thus enhancing disease severity, and it is not essential for the induction and maintenance of pathogenic inflammatory T_H1 cells, whereas the maintenance of the psoriatic process is produced by IL-12 in an IFN-γ–independent mechanism.

Our results demonstrate that the mean serum levels of IFN-γ were significantly elevated in participants with psoriasis of all severities compared

with unaffected controls ($P<.05$), which supports prior studies.[5,6,14] Chodorowska[5] found a significant increase in plasma IFN-γ levels in 27 participants with psoriasis compared with controls (178.7 ± 11.9 pg/mL vs 139.6 ± 7.9 pg/mL, respectively) before treatment ($P<.05$). Somewhat lower plasma IFN-γ levels were measured in participants with psoriasis in the study conducted by Chodorowska[5] compared to participants in our study, which may be explained by the more severe clinical presentation of our participants. Szegedi et al[6] also detected a significant elevation in serum IFN-γ levels in 18 participants with moderate to severe psoriasis vulgaris (PASI score, 20.1 ± 4.5) compared with 10 healthy controls (35.0 ± 47.0 pg/mL vs 4.9 ± 6.4 pg/mL, respectively)($P<.05$) but did not measure the differences in serum IFN-γ levels based on severity of psoriasis.

The current study detected a substantial difference in serum IFN-γ levels in participants with different disease severities, with the highest levels in participants with erythrodermic and severe plaque psoriasis. Notably, participants with erythrodermic psoriasis showed markedly higher serum IFN-γ levels compared with participants with mild to moderate plaque psoriasis and severe plaque psoriasis. In a small study of 10 participants with psoriasis, cytokines related to T_H1 and T_H2 cells were measured and compared with controls.[15] Cytokines related to T_H2 lymphocytes (IL-4, IL-5, IL-6, and IL-10) generally were decreased or similar to controls. As for T_H1 cytokines (IL-2, IL-12, IFN-γ), IFN-γ was substantially increased in participants with psoriasis compared with controls and correlated with disease severity. Surprisingly, other T_H1 cytokine levels, IL-2 and IL-12, were either normal or decreased, respectively.[15] Arican et al[14] also showed a positive correlation of IFN-γ and a number of cytokines (ie, IL-12, IL-17, IL-18) with disease severity of participants with plaque psoriasis. To our knowledge, no study has compared serum IFN-γ levels in erythrodermic psoriasis to other severities of plaque psoriasis.

Fifteen participants received treatment for 16 weeks and were followed for an additional 12 weeks. Despite the differences in the treatment modalities, an improvement in disease condition with a significant decrease in PASI score was accompanied by a significant decrease in serum IFN-γ levels ($P<.05$), which was especially notable in the erythrodermic and severe plaque psoriasis groups. Chodorowska[5] reported a decrease in serum IFN-γ and tumor necrosis factor α levels after successful treatment with dithranol ointment. Piskin et al[16] showed a decrease in both psoriatic lesions and serum IFN-γ levels after successful NB-UVB therapy, denoting that part of the immunomodulatory effect of phototherapy on psoriasis is through inhibition of IFN-γ production, which may occur either directly or through inhibition of IFN-γ stimulators such as IL-12, IL-18, or IL-23.[17] In another study, there was no decrease in lesional skin IFN-γ levels after successful treatment with either cyclosporin A or methotrexate.[18] The difference in results between the latter study and our study needs further evaluation.

Moreover, in our study, treated participants with serum IFN-γ levels that did not dramatically decrease had a shorter remission period (≤12 weeks) compared with those who showed a significant decrease in serum IFN-γ levels (>12 weeks). This finding could raise the idea of using serum IFN-γ levels as an indicator for the patient's relapse, which will occur in a matter of weeks and probably help to intervene at the right time.

Although serum IFN-γ levels were measured in a small number of participants before and after treatment in our study, the substantial decrease of serum IFN-γ levels encourages further studies on a larger group of participants to evaluate the treatment modality that is most efficient in decreasing serum IFN-γ levels.

Conclusion

The current study further underscores the central role of IFN-γ in psoriasis and encourages the development of anti–IFN-γ biologic therapy in the treatment of psoriasis and other T_H1-mediated diseases.

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