ANNALES
UNIVERSITATIS MARIE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LVIII, N 1, 59 SECTIO D 2003

Chair and Department of Dermatology, Medical University of Lublin

GRAŻYNA CHODOROWSKA, DOROTA CZELEJ,
DOROTA KRASOWSKA, ALDONA PIETRZAK

Plasma activity of Interleukin-10 in drug-induced cutaneous reactions

Adverse drug-induced cutaneous reactions are connected with various types of immune response. Among the cytokines being mediators of this response, interleukin-10 (IL-10) seems to be of special interest because of its role in redressing the disturbed immune homeostasis. IL-10 plays pivotal regulatory role in cytokine network due to the inhibitory influence upon the cell-type immune reactions and promoting humoral response (1–7). IL-10 is mostly produced by activated Th2 lymphocytes, B cells, monocytes/macrophages, fibroblasts and keratinocytes (2, 3, 4, 6). The ability of epidermal cells to express IL-10 increases considerably after exposure to ultraviolet rays (1). IL-10 is regarded as an important factor in complex cross-regulation between different subpopulations of T lymphocytes (2, 6). Antiinflammatory and immunosupressive activity of IL-10 is connected with its powerful direct influence on two key cells in immune and inflammatory reactions: T lymphocytes and monocytes/macrophages and two pleiotropic cytokines: IFN-γ and TNF-α (1, 6, 7). Thus, IL-10 is capable of controlling indirectly all network of secondary cytokines released by various cell types (1, 6, 7). As a funtional TNF-α inhibitor, IL-10 is engaged in compensatory antiinflammatory response, which was found in rheumatoidal arthritis (7). Moreover, in accordance with this role, IL-10 can block the IL-6 release by T lymphocytes through the IL-2-independent mechanism (2). So, IL-10 by inhibiting IL-6 synthesis can indirectly decrease the acute phase protein production.

A remarkable influence of IL-10 upon the humoral response through promoting growth and differentiation of activated B lymphocytes is especially worth to stress (3, 6). IL-10 in cooperation with other cytokines, like TGF-β, acts as a stimulating factor for B cells (3, 6). As a powerful inductor of B cells function, IL-10 increases expression of MHC II class antigens on these cells, stimulates their proliferation, differentiation and immunoglobulin synthesis, especially acting together with IL-4 (6). So, IL-10 seems to be multifunctional regulator of T cells activity, inductor of B cells, mediator inactivating monocytes/macrophages and a factor capable of down-regulating expression of proinflammatory cytokines (6).

The aim of the study was to evaluate the intensity of compensatory antiinflammatory response in the course of drug-induced skin reactions, expressed by plasma activity of IL-10 in the acute stage and clearing of skin symptoms.

MATERIAL AND METHODS

126 patients with drug-induced skin reactions were included into the study. Among them were 61women and 65 men, aged from 18 to 77 years, mean age 41.5 years. The control group consisted of 30 healthy volunteers of appropriate age. All patients were subdivided into 6 following groups: 1) maculopapular eruptions (ME) – 40 patients. 2) drug-induced urticatia (DU) – 33 patients, 3) erythema multiforme (EM) – 24 patients, 4) erythema multiforme + erythema nodosum (EMN) – 6 patients, 5) hyperergic vasculitis (HV) – 14 patients, 6) Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) – 9 patients.

Blood samples were taken from all the patients: a) during the acute stage of disease, before the treatment was administered; b) after clearing of skin lesions following effective treatment.

Measurement of IL-10 concentrations. An enzyme-linked immunosorbent assay (ELISA) was used to detect and quantify the presence of IL-10 in plasma. The kits for ELISA were provided by Endogen Inc.USA. The measurements were done in duplicates according to the instructions included in the assays. The obtained data were submitted to statistical analysis. Average (M), median (Me), standard deviation (SD), standard error (SE) and variation coefficient (V%) were evaluated. Signficance of differences between the means was tested by the Student's t-test and Mann-Whitney's test

RESULTS

Mean plasma levels of IL-10, measured in the acute stage in each of 6 drug-induced skin reactions, were highly significantly elevated in comparison with control ($p<0.001$) (Tab. 1). Clinical recovery was, connected with deep decrease of IL-10 level in all groups of patients, and in ME, EM, DU and HV groups this decrease was highly significant ($p<0.001$), but in EMN ($p<0.01$) and SJS/TEN ($p<0.05$) – significant in comparison with the treatment values before (Tab.1, Fig.1) However, when compared with the control, mean plasma levels of IL-10 remained still highly significantly, or at least significantly (EMN) elevated, despite their deep decrease observed after treatment (Tab.1, Fig.1). The highest values of IL-10 were observed in EMN group before treatment, and in SJS/TEN group after treament (Tab.1).

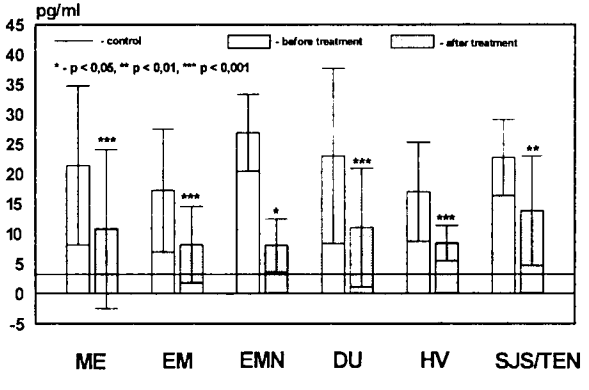

Fig. 1. Plasma concentrantions of IL-10 in 126 patients with drug-induced skin reactions before and after treatment

Table. 1. Plasma concentrantions of IL-10 in 126 patients with drug-induced skin reactions

Patients	Group	Statistical characteristics						Comparison		
		n	M	SD	Min	Max	V%	with control		after vs before treatment
								p	lg%	p
ME	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	40	21.39	13.32	6.10	67.40	62.28	< 0.001	2.83	< 0.001
	P_2	40	10.77	13.26	1.70	67.20	123.16	< 0.001	2.53	
EM	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	24	17.20	10.27	3.20	39.90	59.71	< 0.001	2.73	< 0.001
	P_2	24	8.14	6.37	1.20	25.50	78.21	< 0.001	2.41	
EMN	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	6	26.87	6.43	17.60	36.20	23.93	< 0.001	2.93	< 0.05
	P_2	6	8.02	4.41	3.20	14.80	54.98	< 0.01	2.40	
DU	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	33	22.97	14.65	4.60	65.20	63.77	< 0.001	2.84	< 0.001
	P_2	33	10.98	9.90	0.90	42.50	90.15	< 0.001	2.54	
HV	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	14	16.96	8.28	6.20	35.40	48.22	< 0.001	2.73	< 0.001
	P_2	14	8.37	2.96	2.70	11.60	35.41	< 0.001	2.43	
SJS/TEN	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	9	22.68	6.39	13.90	30.00	28.18	< 0.001	2.85	< 0.01
	P_2	9	13.79	9.13	0.70	23.90	66.29	< 0.001	2.64	
All patients	C	30	3.14	1.80	0.60	7.60	57.35			
	P_1	126	20.87	12.19	3.20	67.40	58.42	< 0.001	2,76	< 0,001
	P_2	126	10.14	9.85	0.70	67.20	97.13	< 0.001	2,13	

c – control, p_1 – patients before treatment, p_2 – patients after treatment

The lowest values before treatment were observed in HV group, and in EMN group after treatment. Before treatment, statistically significant differences ($p<0.05$) in IL-10 mean values were observed between EMN and EM, HV groups, and between SJS/TEN and HV groups. After treatment the differences of IL-10 plasma levels among 6 groups of patients were not statistically significant ($p>0.05$).

DISCUSSION

Results of this study indicate high increase of the IL-10 mean plasma concentration in the whole group of 126 patients in the acute stage of drug-induced skin reactions. Moreover, despite the deep decrease of IL-10 level at recovery, it still remained highly elevated in comparison with the values found in the healthy control. It is worth to stress. That clearing of the disease symptoms due to effective treatment was connected with highly significant (ME, EM, DU, HV) or significant (EMN, SJS/TEN) decrease of mean IL-10 concentrations in comparison with the before treatment values. In accordance with the role of IL-10 as the cytokine promoting the humoral response, IL-10 concentrations in urticaria were distinctly high, higher then in hyperergic vasculitis, erythema multiforme or maculopapular eruptions, although the differences were not statistically significant. It seems of special interest that IL-10 concentrations were already elevated in the acute stage of drug-induced diseases and what is more, they did not return to the control values simultaneously with the clinical clearing. This observation is in agreement with the assumed regulatory role of IL-10 in immune system.

In our study, the elevated values of IL-10 in the acute stage of drug-induced skin reactions exceeded low concentrations observed in the healthy people more than 6.5 times. It means that, acute inflammation developing in the skin can mobilize the compensatory antiinflammatory response acting as a negative feed-back leading to restoration of the disturbed immune homeostasis. Similarly, Yawalkar et al.(8) observed elevated values of IL-10 in the acute stage of maculopapular drug-induced eruption and, what is more, decrease to the undetectable values not earlier than two months after clearing of disease. These authors also observed that the increase of IL-10 level in their patient was simultaneous with elevation of its antagonist - IL-6 in the peripheral blood (8). A study of IL-10 activity in immune-based diseases connected with predominance of humoral response, like systemic scleroderma, showed a several fold elevation of this protein level in the patients when compared with low values observed in healthy people([4). Other authors found that in the acute stage of the Leishmania donovani infection IL-10 is released in a larger amount than in the stage of clearing (6). So, it can support the opinion that induction of inflammation connected with infection causes simultaneous mobilization of antagonistic response leading to limiting its development and restoring homeostasis disturbed in the course of disease.

CONCLUSIONS

1. Plasma activity of IL-10 was highly elevated in patients with drug-induced skin reactions in the acute stage and despite after-treatment decrease it remained still high during the recovery.

2. Compensatory antiinflammatory response in the course of drug-induced cutaneous reactions is early induced and lasts longer than clinical symptoms.

REFERENCES

1. Grewe M. et al: Interleukin-10 production by cultured human keratinocytes: regulation by ultraviolet A1 radiation. J.Invest.Dermatol., 104, 3, 1995.

2. Hempel L., et al: Interleukin-10 directly inhibits the Interleukin-6 production in T-cells. Scand.J.Immunol., 41, 462, 1995.
3. Kozioł-Montewka M.: Ocena systemu cytokin, rozpuszczalnych receptorów i powierzchniowych cząstek sygnalizacyjnych w aspekcie zaburzeń immunologicznych u chorych z przewlekłą niewydolnością nerek. Praca habilitacyjna, Akademia Medyczna w Lublinie, 1997.
4. Kucharz E.J. et al: Elevated serum level of Interleukin-10 in patients with systemic sclerosis. Clin.Rheumatol., 16, 6, 638, 1997.
5. Mitra R.S. et al: Psoriatic skin-derived dendritic cell function is inhibited by endogenous Interleukin-10. J.Immunol., 154, 2668, 1995.
6. Robak T.: Biologia i farmakologia cytokin. PWN, Warszawa-Łódź 1995.
7. Sebbag M. et al: Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of TNF-α, but not IL-10. Eur.J.Immunol., 27, 624, 1997.
8. Yawalkar N. et al: Elevated serum levels of interleukins 5, 6 and 10 in a patient with drug-induced exanthem caused by systemic corticosteroids. J.Am.Acad.Dermatol., 39, 790, 1998.

SUMMARY

Plasma concentrations of interleukin-10 (IL-10) were examined in 126 patients with drug-induced cutaneous reactions: maculopapular eruptions (ME), erythema multiforme (EM), erythema multiforme coexisting with erythema nodosum (EMN), drug-induced urticaria (DU), hyperergic vasculitis (HV), Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Activity of the cytokine was measured using the immunoenzymatic ELISA method: a) in the acute stage of disease before treatment was administered, and b) after clearing of skin lesions, after treatment. In the acute stage of disease highly elevated mean concentrations of IL-10 in all 6 groups of patients were found ($p<0.001$) in comparison with the control. After clearing of clinical symptoms IL-10 concentrations were decreased highly significantly (ME, EM, DU, HV) or significantly (EMN, SJS/TEN) in comparison with the values before treatment, but remained still considerably elevated ($p<0.001$; $p<0.01$) when compared with the healthy control. Results of this study indicate that the compensatory antiinflammatory response, expressed as elevated IL-10 activity, is induced as early as in the acute stage of skin lesions and lasts longer than clinical symptoms of drug-induced cutaneous reactions.

Osoczowa aktywność interleukiny-10 w skórnych reakcjach polekowych

Badano stężenia interleukiny-10 (IL-10) u 126 pacjentów z polekowymi chorobami skóry: osutkami plamistogrudkowymi (ME), rumieniem wielopostaciowym (EM), rumieniem wielopostaciowym współistniejącym z rumieniem guzowatym (EMN), ostrą pokrzywką (DU), hyperergicznym zapaleniem naczyń (HV) oraz zespołem Stevens-Johnsona i toksyczną nekrolizą naskórka (SJS/TEN). Aktywność cytokiny oznaczano w osoczu przy pomocy metody immunoenzymatycznej ELISA: a) w ostrym okresie choroby przed rozpoczęciem leczenia oraz b) po ustąpieniu zmian chorobowych i zakończeniu leczenia. Stwierdzono znaczne podwyższenie średniego stężenia IL-10 we wszystkich badanych grupach przed leczeniem ($p<0.001$) w porównaniu z grupą kontrolną. Po ustapieniu objawów klinicznych stężenia IL-10 obniżyły się wysoce istotnie (ME, EM, DU, HV) lub istotnie (EMN, SJS/TEN) w stosunku do wartości przed leczeniem, lecz nadal pozostały znacznie podwyższone ($p<0,001$, $p<0,01$) w porównaniu ze stężeniami stwierdzanymi u ludzi zdrowych. Uzyskane wyniki wskazują na to, że w przebiegu skórnych reakcji polekowych dochodzi do uruchomienia kompensacyjnej odpowiedzi przeciwzapalnej, wyrażonej przez podwyższoną aktywność IL-10 już w ostrym okresie zmian chorobowych i utrzymywania się jej dłużej niż objawy kliniczne.