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Interleukin-6 and some acute phase proteins plasma activity in drug-induced maculopapular eruptions

Maculopapular eruptions are the most common among the drug-induced cutaneous adverse reactions (1, 5, 8). They are observed as morbilliform, scarlatiniform, and not unusually as generalized erythematous and papular lesions covering extensive body area (5). Skin symptoms develop after several days following the onset of the culprit drug intake, but usually not later than after two weeks (5). The majority of authors consider that the delayed-type immune mechanism is involved in the pathogenic events of maculopapular drug-induced eruptions (9, 10,15). This belief is supported not only by the time of onset and release of typeTh1 cytokines (e.g. IFN-γ) being observed, but also by the possibility to confirm the culprit drugs by patch tests (9, 10, 15). Intensive cutaneous inflammation suggests that the acute phase reaction can be initiated. Among the inflammatory mediators, IL-6 plays the main role as activator of this general homeostatic response (3, 14).This cytokine is capable of inducing synthesis of all acute phase proteins, including C-reactive protein (CRP) and α-2 macroglobulin (α-2MG) (3,14). IL-6 seems to be of special interest in drug-induced eruptions, because it is the powerful regulator of activation, proliferation and differentiation of T lymphocytes into cytotoxic effector cells (3, 7, 14). IL-6 is also capable to influence the growth of B cell, immunoglobulins' production, and macrophage activation (14). Wide spectrum of biological activity of IL-6 enables this cytokine to take part in many various inflammatory and immune events in the skin, and especially in T lymphocyte activation, proliferation, differentiation and cytokine production (3, 7, 12, 14). Among the large group of the acute phase proteins controlled by IL-6, C-reactive protein is specially interesting due to a variety of its biological activity. Identification of damaged cells and their products (nuclear debris, remains of cellular membranes) in the focus of inflammation or necrosis, followed by complement activation and facilitation of phagocytosis are the main abilities of CRP leading to absorption of inflammatory infiltration and damage repair (11, 12). CRP synthesis is controlled not only by IL-6 but also by other proinflammatory cytokines, such as IL-1, TNF-α, IFN-γ (3,12,14) which possibly take part in pathogenetic events in drug-induced skin diseases.

α-2 Macroglobulin has ability to bind to own and foreign proteins taking role of protein-carrier (2, 4, 6) α -2 MG proved to be a carrier of many immune mediators, including cytokines and growth factors (2, 4, 6) taking part in ensured efficient concentrations of these active agents, necessary in interacting with their membrane receptors (4, 6). Thus α -2 MG is one of the paracrine regulators of growth and function of various cell types, including B and T lymphocytes, fibroblasts and other cells (2, 4, 6). It is believed that regulation of distribution and activity of many cytokines is the main biological function of α-2 MG (2, 4, 6).

The aim of the study was to evaluate the intensity of inflammatory and immune response in drug-induced maculopapular eruptions expressed as activity of IL-6 and stimulated by this cytokine acute phase proteins.

MATERIAL AND METHODS

40 patients with drug-induced maculopapular eruptions were included into the study. Among them were 16 women and 24 men. Mean age of the group was 45.3 years, range from 18 to 74. All the patients had generalized eruption covering extensive skin areas. The examined patients have taken the culprit drugs three to12 days before their exantem appeared. Six patients admitted taking only one drug, 34 patients have received at least two offending agents. In the examined group the most frequent causative drugs were various antibiotics (but especially ampicillin, amoxicillin), analgetics/antipyretics, and nonsteroidal antiinflammatory drugs.

The blood samples were taken from the patients: a) during the acute stage of disease, before the treatment was administered; b) after clearing of skin lesions following the effective treatment. Regression of clinical symtoms was achieved after 10 to 15 days of treatment. Control group consisted of 30 healthy volunteers in appropriate age.

Measurements of protein concentrations. An enzyme-linked immunosorbent assay (ELISA) was used to detect and quantify the presence of the selected proteins in plasma. The kits for ELISA were provided by Endogen Inc. USA (IL-6), Immunodiagnostic, Germany (α -2 MG) and Eucardio Laboratory, USA (CRP). The measurements were done in duplicates according to the instructions included in the assays.

Statistical methods. The obtained data were put to statistical analysis. Average (M), median (Me), standard deviation (SD), the mean error of the average (SE) and variation coefficient (V%) were evaluated. Significance of differences between the averages was tested by the Student's t-test, c-Cochran's-Cox's test and Mann-Whitney's test.

RESULTS

In the acute stage of maculopapular eruptions before the treatment was introduced the considerable increase of plasma levels of IL-6, CRP and α-2 MG ($p < 0.001$) was observed in comparison with the control group (Table 1, Fig. 1). Efficient treatment caused changes of the proteins' activity. After clearing of the skin lesions the deep decrease of protein concentrations in peripheral blood was observed. IL-6 and α-2 MG plasma concentrations were lowered towards the control values ($p > 0.05$), but CRP mean plasma concentration despite its deep decrease was still highly significantly elevated ($p < 0.001$) when compared with control values (Fig. 1). It is worth to stress that IL-6, CRP and α-2 MG plasma concentrations measured when clearing of disease was achieved were highly significantly lowered in comparison with acute stage, before the treatment was administered ($p < 0.001$) (Fig. 2).

Table 1. Plasma concentration of IL-6, CRP and α-2 MG in 40 patients with drug-induced maculopapular eruptions; C – control, P_1 – patients before treatment, P_2 – patients after treatment

Protein	Group	Statistical characteristics					Comparison			
							before treatment	after treatment	with control	
		Min	Max	M	SD	V%			p	lg%
IL – 6 (pg/mL)	C	0	5.6	1.83	1.34	73.21				
	P_1	0	42.00	8.93	10.29	115.21	$p < 0.001$		$p < 0.001$	2.68
	P_2	0	12.60	2.58	3.19	123.61			$p > 0.05$	2.14
CRP (mg/L)	C	0	0.86	0.29	0.30	102.46				
	P_1	2.42	20.00	10.72	5.74	48.95	$p < 0.001$		$p < 0.001$	3.56
	P_2	0	7.06	2.31	1.80	77.81			$p < 0.001$	2.90
α - 2MG (mg%)	C	30.0	190.00	129.53	42.87	33.10				
	P_1	118.00	740.00	574.55	160.00	27.85	$p < 0.001$		$p < 0.001$	2.64
	P_2	36.00	640.00	202.40	148.46	73.35			$p > 0.05$	2.19

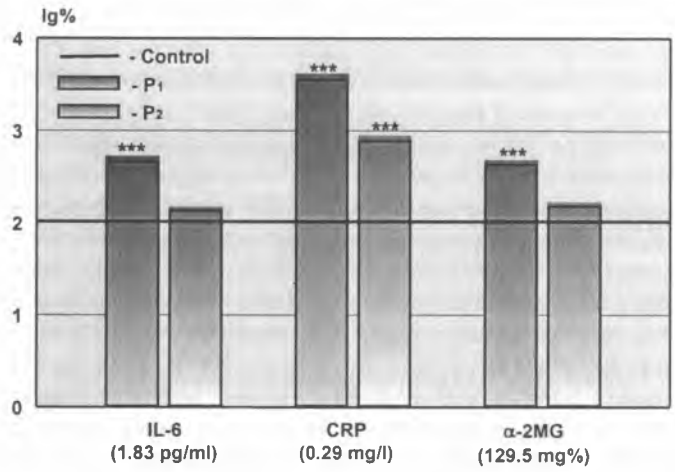

Fig. 1. Plasma concentrations of IL-6, CRP and α-2 MG in 40 patients with drug-induced maculopapular eruptions expressed as lg% of the control values; 1) control values are expressed below the respective bars, 2) significance of differences in comparison with control expressed as: ***p < 0.001; 3) P_1 – patients before treatment, P_2 – patients after treatment

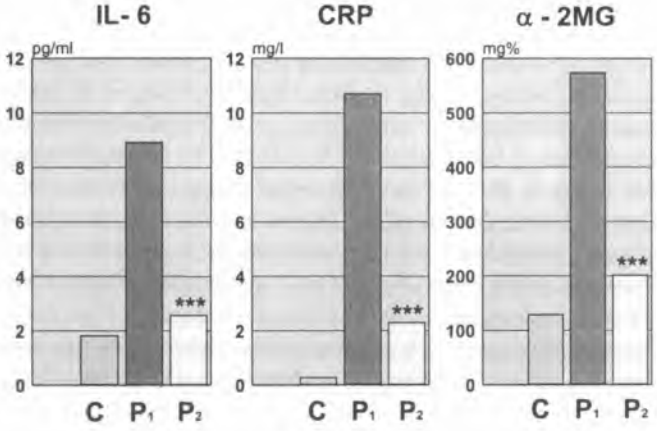

Fig. 2. Plasma concentrations of IL-6, CRP and α-2 MG in 40 patients with drug-induced maculopapular eruptions; 1) significance of differences before and after treatment (P1 vs P2) expressed as: *** p < 0.001; 2) C – control, P_1 – patients before treatment, P_2 – patients after treatment

DISCUSSION

Results of our study indicate that the activity of investigated proteins can change together with changes in the clinical stage of the patients suffering from the maculopapular exantems. Moreover, activation of the acute phase proteins by IL-6 can account for existence of general symptoms of inflammation in severe drug-induced reactions. Quick return of IL-6 level towards the control values after clearing of inflammation is a characteristic phenomenon, observed also by other authors (13). CRP is regarded as the most dynamic indicator of inflammation, whose concentration can increase up to 100 and more times (11). In this study, 37-fold increase of CRP in the acute stage of disease was

observed in comparison to control values. In the examined patients the total normalization of CRP level was not observed. It is worth to stress that in this study elevated concentrations of CRP after treatment were still high.The mean CRP plasma level remained eightfold increased above the normal values. The obtained results support the belief that CRP is very sensitive despite non-specific indicator of inflammation in the course of the diseases of various origin (11). The presence of the elevated CRP concentrations in the peripheral blood can be the result of interaction among proinflammatory cytokines, their receptors and suppressive factors in the course of the disease. Unique relation links α-2 macroglobulin with interleukin-6. IL-6 is the main inducer of α-2 MG synthesis, but on the other hand α-2 MG is the carrier protein for IL-6, so both these proteins can modulate one another's activity. Thus, changes of α-2 MG activity in the peripheral blood can reflect many complex phenomena during inflammation. It seems that α-2 MG may be involved in pathogenic processes of drug-induced skin reactions, not only as the acute phase protein but perheps mostly as the regulator of cytokines' distribution and activity.

Our study revealed large contribution of antibiotics, especially ampicillin and amoxicillin in inducing maculopapular eruptions. This observation is supported by the literature data, because other authors have also observed, that ampicillin, other penicillins and analgetics and antiinflammatory drugs were the most frequent culprit agents (5, 8).

CONCLUSIONS

1. In the course of drug-induced maculopapular eruptions the acute phase response can be mobilized.

2. Clinical clearing is connected with significant decrease of Interleukin-6, C-reactive protein and α-2 macroglobulin concentrations in the peripheral blood of patients.

3. Increased activities of the examined proteins are observed longer than clinical symptoms of drug-induced maculopapular eruptions.

REFERENCES

1. Bigby M.: Incidence, prevalence and the rates of cutaneous reactions to drugs. JEADV, 14, 435, 2000.
2. Birkenmeier G., Frank R.: Plasma concentration of total and transformed α-2 macroglobulin in systemic sclerosis. Arch. Dermatol. Res., 299, 405, 1996.
3. Borden E. C., Chin P.: Interleukin-6: a cytokine with potential diagnostic and therapeutic roles. J. Lab. Clin. Med., 123, 824, 1994.
4. Borth W.: α-2 Macroglobulin, a multifunctional binding protein with targeting characteristics. FASEB J., 6, 3345, 1992.
5. Braun-Falco O. et al: Reactions to medications [In:] O. Braun-Falco et al. (ed.): Dermatology, Springer-Verlag, 403, Berlin–Heidelberg–New York, 2000.
6. Gonias S. L.: α-2 Macroglobulin: a protein at a surface of fibrinolysis and cellular growth regulation. Exp. Hematol., 20, 302, 1992.
7. Hempel I. et al.: Interleukin-10 directly inhibits Interleukin-6 production in T-cells. Scand. J. Immunol., 41, 462, 1995.
8. Ibia E. I. et al.: Antibiotics rashes in children. Arch. Dermatol., 136, 849, 2000.
9. Iliev D., Elsner P.: Generalized drug reactions due to papaya juice in throat lozenges. Dermatology, 194, 364, 1997.

10. Koga T. et al.: Serum interferon-γ level in a patient with carbamazepine-induced erythroderma. Contact Dermatitis, 33, 275, 1995.
11. Kolb-Bachofen V.: Review on the biological properties of C-reactive protein. Immunobiol.,183, 133, 1991.
12. Nakajima Y. et al.: Induction of the acute phase proteins by recombinant human interleukin-6 in calves. Vet. Immunol. Immunopathol., 35, 385, 1993.
13. Robak T.: Biologia i farmakologia cytokin. PWN, Warszawa–Łódź 1995.
14. Wiliams I. R., Kupper T. S.: Immunity at the surface: homeostatic mechanisms of the skin immune system. Life Sci., 58, 1485, 1996.
15. Yawalkar N. et al.: Elevated serum levels of interleukins 5, 6 and 10 in a patient with drug--induced exanthem caused by corticosteroids. J. Am. Acad. Dermatol., 39, 790, 1998.

SUMMARY

The evaluation of inflammatory response in drug-induced maculopapular eruption was the aim of the study. Plasma concentrations of interleukin-6 (IL-6), C-reactive protein (CRP) and α-2 macroglobulin (α-2 MG) were measured in 40 patients with maculopapular eruptions using the immunoenzymatic ELISA method in acute stage of disease and after clearing of skin lesions due to effective therapy. In the acute stage of the disease mean plasma levels of the examined proteins were highly significantly elevated ($p < 0.001$) in comparison with healthy control. Regression of the clinical symptoms was connected with the deep decrease of protein concentrations in the peripheral blood. After treatment the plasma levels of IL-6 and α-2 MG were lowered towards the control values ($p > 0.05$), but CRP despite its deep decrease was still highly significantly elevated ($p < 0.001$) in comparison with control. The results of this study indicate that in drug-induced maculopapular eruptions the acute phase response can be initiated and that the observed increased activity of the examined proteins lasts longer than the clinical symptoms of the disease.

Osoczowa aktywność interleukiny-6 oraz wybranych białek ostrej fazy w plamistogrudkowych osutkach polekowych

Celem pracy była ocena odpowiedzi zapalnej w przebiegu plamistogrudkowych osutek polekowych. Badano stężenia osoczowe interleukiny-6 (IL-6) oraz białka C-reaktywnego (CRP) i α-2 makroglobuliny (α-2 MG) u 40 pacjentów, posługując się metodą immunoenzymatyczną ELISA. Aktywność badanych białek oznaczano w ostrym okresie choroby przed rozpoczęciem leczenia oraz po ustąpieniu zmian chorobowych i zakończeniu leczenia. Stwierdzono wysoce statystycznie istotne podwyższenie średnich stężeń badanych białek w porównaniu z grupą kontrolną ($p < 0,001$). Ustąpienie objawów klinicznych wiązało się ze znacznym obniżeniem stężeń IL-6, CRP i α-2 MG we krwi obwodowej. Po leczeniu stężenia osoczowe IL-6 i α-2 MG obniżyły się w kierunku wartości kontrolnych ($p > 0,05$), natomiast poziom CRP, pomimo znacznego obniżenia, był nadal wysoce statystycznie istotnie podwyższony ($p < 0,001$) w porównaniu z kontrolą. Uzyskane wyniki wskazują na to, że w polekowych osutkach plamistogrudkowych może dojść do pobudzenia odpowiedzi ostrej fazy i że zwiększona aktywność badanych białek trwa dłużej niż kliniczne objawy choroby.